[CONTRIBUTION FROM ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

Reactions of Some Ester Alkaloids and Related Synthetic Compounds with the Phenyl Grignard Reagent

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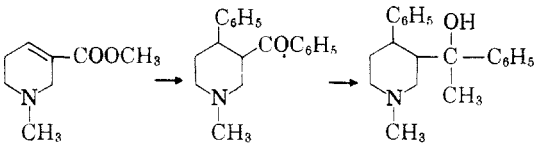
Reactions of arecoline (I), cocaine (VI), the methyl ester of anhydroecgonine (IX), and pilocarpine (XIII) with phenylmagnesium bromide have been carried out and the products have been subjected to further transformations. In addition, the two stereoisomeric 3-aceto-1,4-dimethyl-4-hydroxypiperidines (XI) and three simple imidazole esters XVI, XVII, and XVIII have been treated similarly. The stereochemistry of several of the products is discussed and their preliminary pharmacological assay is reported.

In order to prepare a number of basically substituted benzhydrols for examination in connection with their pharmacological activity on the central nervous system, it seemed appropriate to use as starting materials, suitably substituted alkaloids which possess physiological activity in their own right. Arecoline was chosen as one alkaloid which fulfilled these requirements. Treatment of arecoline (I) with excess phenylmagnesium bromide in refluxing ether gave a 36% yield of a solid base, m.p. 115–116°, which was not the expected carbinol, but rather an isomeric ketone II formed by both simple and conjugate addition to the unsaturated ester. The ketonic nature of the product was established by infrared analysis, and by the fact that reaction with methylmagnesium iodide led to a carbinol IV, m.p. 86–87°. Furthermore, when II was treated with concentrated hydrobromic acid



in an attempt to effect cyclodehydration to the corresponding pyridindene derivative,[1] the only product isolated (72% yield) was an isomeric ketone III, m.p. 62–63°. That compounds II and III bear a *cis-trans* relationship to each other becomes obvious from Zimmerman's[2] experience in the analogous cyclohexane series. He found that the main kinetically favored product formed in the reaction of phenyl Grignard reagent with 1-benzoylcyclohexene is *cis*-1-benzoyl-2-phenylcyclohexane; but that, when equilibrium conditions are permitted, the *cis* isomer is converted quantitatively to the thermodynamically more stable *trans* form. Also, in accord with his findings we observed that compound II decolorizes a solution of bromine in hot glacial acetic acid whereas the isomeric III does not. Thus, with considerable confidence, the higher melting isomer II can be assigned the *cis* configuration and the lower melting III the *trans*. It follows that the two carbinols IV, m.p. 86–87°, and V, m.p. 142–143°, although bearing an inverse melting point relationship with respect to II and III, actually maintain the same steric relationship, for if steric integrity had not been maintained during the addition of methyl Grignard reagent, only one product or at least the same mixture of products would have been obtained from both II and III. The fact that only one of the two possible racemic mixtures was obtained in each case is interesting but not unexpected. It is also of interest to note the incidental observation that the infrared absorption band of the carbonyl group in the *cis* ketone II is at 5.88μ whereas that of the *trans* ketone III is at a significantly longer (5.92μ) wave length.

In addition to the hydrobromic acid treatment already mentioned, other methods were used in attempting to cyclodehydrate the *cis* ketone II. Treatment either with refluxing 65% sulfuric acid or with polyphosphoric acid led to III as the only isolable product. From anhydrous hydrogen fluoride at room temperature II was recovered unchanged. Aluminum chloride in tetrachloroethylene led only to destruction of the material.

Two publications pertinent to the present work appeared during and after its completion. Lyle, Perlowski, and Lyle[3] treated arecoline (I) with phenyllithium and obtained a 74% yield of the expected 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenyl carbinol. Plati, Ingberman, and Wenner[4] treated arecoline with phenylmagnesium bromide at −10° and obtained a 73% yield of a mixture of the two stereoisomeric modifications of 1-methyl-3-carbomethoxy-4-phenylpiperidine formed by 1,4-addition of one mole of the Grignard reagent. However, no assignment of configuration could be made in their case. In view of the low yield (36%) of II obtained in our work, their results indicate that III must have also been formed in considerable

(1) See J. T. Plati and W. Wenner, *J. Org. Chem.*, **20**, 1412 (1955) and earlier references.

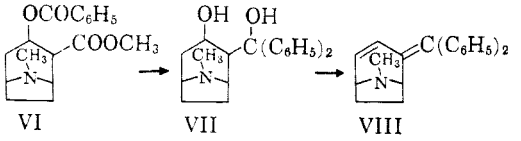
(2) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

(3) G. G. Lyle, E. F. Perlowski, and R. E. Lyle, *J. Org. Chem.*, **21**, 423 (1956).

(4) J. T. Plati, A. K. Ingberman, and W. Wenner, *J. Org. Chem.*, **22**, 261 (1957).

amounts although none was actually isolated from residues of the Grignard reaction. Their work also indicates that the ketone II must arise from primary 1,4-addition of the Grignard reagent to the conjugated ester system.

Attention was next directed to the reaction of cocaine VI with phenylmagnesium bromide. When a large excess of the Grignard reagent was used,

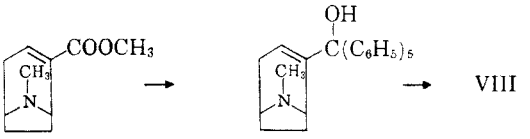


VI VII VIII

the expected glycol VII was isolated in 51% yield as a solid base, m.p. 185–186°. It was further characterized by conversion to a quaternary methomethyl sulfate and by dehydration to the diene VIII. Attempts to effect selective elimination of the tertiary hydroxyl group failed. When the glycol VII was distilled under reduced pressure either with or without added iodine as a catalyst, it was recovered unchanged. When it was distilled from potassium bisulfate or treated with a refluxing solution of hydrochloric acid in acetic acid, only the diene VIII was obtained as a yellow oil, b.p. 201–203° (2.5 mm.). This behavior is readily accounted for by the fact that initial elimination of the tertiary hydroxyl would yield a ring-substituted allylic carbinol which could be expected to dehydrate as readily as the tertiary carbinol. It is interesting to note the radical change in specific rotation observed in going from the glycol VII ($[\alpha]_D^{27}$ −23.5°) to the diene VIII ($[\alpha]_D^{30}$ +548°). Compound VII undoubtedly possesses the same conformation as cocaine which has been elucidated by others.[5]

The diene VIII was further characterized by conversion to a quaternary methiodide, m.p. 281–282° dec., by pK_a measurements and by its ultraviolet absorption spectrum. The pK_a values (measured by potentiometric titration in aqueous methanol) of compounds VI, VII, and VIII are, respectively, 7.6, 7.5, and 7.3. If, even in violation of Bredt's rule, one of the two double bonds were at the bridgehead, the pK_a of the resulting vinylamine would be expected to be much lower rather than of the same order as the pK_a values observed for the two reference substances. Furthermore, the ultraviolet absorption spectrum of VIII in ethanol shows a broad band in the region, 281–283 mμ typical of the 1-phenylbutadiene system[6] and practically identical with the absorption at 281 mμ reported[3] for the analogous diene formed by dehydration of the carbinol obtained by the addition of phenyllithium to arecoline.

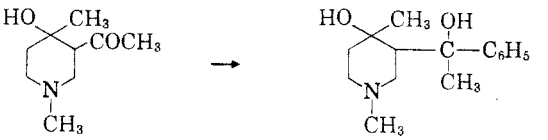
In order to prepare compounds in the tropane series analogous to those obtained from arecoline (I), the methyl ester (IX) of anhydroecgonine was prepared. The literature[7] reports the direct Fischer-esterification of anhydroecgonine by methanol in 70% yield. In the present work only poor yields of IX could be secured by this method. However, a 62% yield of the ester was finally obtained by refluxing the acid in a mixture of methanol and ethylene dichloride in the presence of Amberlite XE-156 resin. Treatment of IX with phenylmagnesium bromide gave a mixture of basic products from which no pure substance could be isolated. How-



IX X

ever, when phenyllithium was substituted for the Grignard reagent a 56% yield of the carbinol X, m.p. 209–210°, was obtained, which showed no carbonyl absorption in the infrared. The compound was characterized further by quaternization and by dehydration to a yellow oil which gave a quaternary methiodide identical in infrared spectrum and specific rotation to the methiodide previously obtained from the diene VIII.

The two synthetic stereoisomers of 3-aceto-1,4-dimethyl-4-hydroxypiperidine (XI), obtained by Mannich and Ball[8] from the reaction of acetone with formaldehyde and methylamine, seemed to provide suitable structures for the purpose of this work. Accordingly, both the α-form of XI, m.p. 130°, and the β-form, m.p. 85–86°, were treated with phenyl-



XI, α and β XII, α and β

magnesium bromide in refluxing benzene. The corresponding glycols XII were obtained in 45% and 11% yields, respectively. The greater reactivity of the α-ketone was further evinced by a tendency, not shown by the β-isomer, to react exothermically during the initial phase of the Grignard reaction. These facts, taken together with the lower melting point of the β-isomer, point to the presence of an intramolecular hydrogen-bonded structure in the latter form, involving the hydroxyl hydrogen and the carbonyl oxygen. The infrared spectra of the two isomers are also consistent with this designation. The α-form, at 0.7% concentration in carbon tetrachloride, shows two hydroxyl

(5) O. Kovacs, G. Fodor, and G. Weiss, *Helv. Chim. Acta*, **37**, 892 (1954).

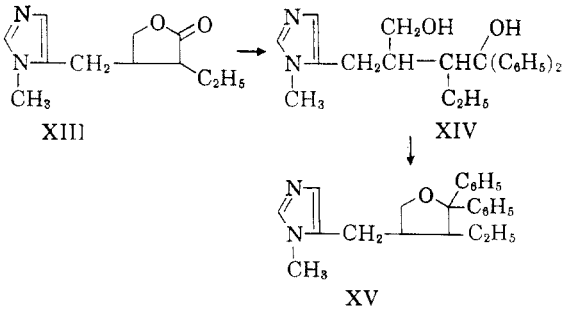
(6) E. A. Braude, E. R. H. Jones, and E. S. Stern, *J. Chem. Soc.*, 1087 (1947).

(7) P. S. Ugryumov, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 997 (1944). *Chem. Abstr.*, **39**, 4616 (1945).

(8) C. Mannich and G. Ball, *Arch. Pharm.*, **264**, 65 (1926).

absorption bands of equal intensity at 2.82μ and 2.88μ. Dilution to 0.1% concentration reduces the intensity of the 2.88-μ band relative to the 2.82-μ band. This indicates that the former band represents absorption by an intermolecularly hydrogen-bonded hydroxyl group which decreases in importance with dilution relative to the non-bonded hydroxyl absorption at 2.82μ. In the β-isomer, on the other hand, only a single more intense band at 2.89μ is in evidence; and, in accord with expectation for intramolecularly hydrogen-bonded hydroxyl absorption, the intensity of this band relative to other absorption does not diminish with dilution nor does non-bonded, hydroxyl absorption (*ca.* 2.8μ) appear. Slight differences in carbonyl stretching frequencies (5.87μ for the β-isomer and 5.85μ for the α-form) also fall in line with the assumption of a greater degree of hydrogen-bonding in the lower melting (β) isomer. Construction of scale models of the two forms reveals that, although the six-membered hydrogen-bonded ring is achievable in the case where the hydroxyl and acetyl are *trans* to each other, the *cis* form lends itself much more readily to such interaction. These circumstances would seem to justify tentative assignment of the *trans* conformation to the higher melting (α) isomer and the *cis* conformation (OH and $COCH_3$ on the same side of the ring) to the lower melting (β) form. Finally, it should be noted that from each of the two forms of XI, as in the preparation of the carbinols IV and V, only one of two possible racemic forms of XII was isolated.

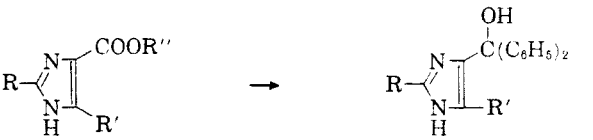
The lactone ring of pilocarpine (XIII) also seemed to provide a suitable functionality for reaction with the Grignard reagent. During the course of the present work, Pourrat[9] reported the reaction of phenylmagnesium bromide with pilocarpine to give the glycol XIV in 70% yield as a solid base, m.p. 290°. However, it was not characterized further. We also obtained the same glycol in 65% yield. It was converted to an optically active hydrochloride and dehydrated by the action of hydrochloric acid in acetic acid to the tetrahydrofuran XV, isolated as the hydrochloride. The structure of



XIII XIV XV

XV was indicated by the fact that its infrared spectrum showed no hydroxyl absorption and no sign of the presence of aliphatic unsaturation. Thus, XV bears a close structural relationship to pilocarpine in which the carbonyl oxygen atom has been replaced by two phenyl groups. It is interesting to note that, in going from XIII to XIV to XV, the specific rotations of the corresponding hydrochlorides in aqueous solution change from +91° to −145° to +156°.

Finally, the three synthetic imidazolecarboxylic esters, XVI, XVII, and XVIII were converted to the corresponding carbinols, XIX, XX, and XXI by treatment with phenylmagnesium bromide. An attempt to prepare the quaternary methiodide



XVI, R = R′ = H; R″ = CH_3
XVII, R = H; R′ = CH_3; R″ = CH_3
XVIII, R = R″ = CH_3; R′ = H

XIX, R = R′ = H
XX, R = H, R′ = CH_3
XXI, R = CH_3; R′ = H

of XX resulted in substitution at the nitrogen atom to give the quaternary salt of the corresponding *N*-methyl derivative.

Pharmacology. Most of the compounds prepared in this work were tested for antagonistic activity against the tremor-producing effects of Tremorine[10] in mice. Only compounds II and VIII were appreciably active, providing complete protection at subcutaneous doses of 10 and 20 mg./kg., respectively. It is interesting that III, the stereoisomer of II, provided only partial protection even at a dose of 50 mg./kg.

In the test for antagonism against acetylcholine-induced spasm of the isolated rabbit ileum only one tertiary amine, VIII, possessed appreciable activity of the order of one-tenth that of atropine. The quaternary salts of II, VIII, and X were, respectively, one-third, one-half, and one-third as active as atropine. All others tested were less than one percent as active.

EXPERIMENTAL

Reaction of arecoline (I) *with phenylmagnesium bromide. Preparation of II.* To a stirred solution of approximately 43 g. (0.24 mole) of phenylmagnesium bromide in 300 ml. of dry ether was added in several portions, 15 g. (0.06 mole) of powdered arecoline hydrobromide.[11] The mixture was stirred and heated under reflux for 2 hr. and allowed to stand overnight. To the stirred reaction mixture cooled in ice was added dropwise an aqueous solution of ammonium chloride. The ether layer was then separated and extracted with dilute hydrochloric acid. The acid extract was cooled in ice and made alkaline by the addition of a 40% aqueous potassium hydroxide solution. The precipitated oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an

(9) H. Pourrat, *Bull. soc. chim. France*, 827 (1955).

(10) G. Everett, L. Blockus, and I. Shepperd, *Science*, **124**, 79 (1956).

(11) Obtained from the Inland Alkaloid Co., Tipton, Ind.

oily residue which crystallized to a waxy solid (11 g.). Two recrystallizations from cyclohexane gave 6 g. (36%) of pure II, m.p. 115–116°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01; O, 5.74. Found: C, 81.52; H, 7.34; N, 5.07; O, 5.61.

The *methiodide* of II, m.p. 217–218° (dec.), was prepared by treatment of a sample of II with excess methyl iodide in methyl ethyl ketone followed by two recrystallizations of the resulting precipitate from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{24}INO$: C, 57.01; H, 5.74; N, 3.32. Found: C, 57.18; H, 6.04; N, 3.30.

Isomerization of II *to* III. A mixture of 10 g. of compound II and 60 ml. of 48% aqueous hydrobromic acid was refluxed gently overnight and then poured into cold water. The mixture was made alkaline by the careful addition of excess solid sodium carbonate and the resulting oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil which solidified on trituration with hexane (Skellysolve B). Two recrystallizations from hexane gave 7.2 g. (72%) of compound III, m.p. 62–63°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01; O, 5.74. Found: C, 81.72; H, 7.70; N, 4.83; O, 5.77.

III *Hydrochloride*, m.p. 230–231° (dec.), from ethanol–ether.

Anal. Calcd. for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; N, 4.44. Found: C, 72.17; H, 7.13; N, 4.40.

Addition of methyl Grignard to the ketones II *and* III. *Preparation of* IV *and* V. To a stirred solution of methylmagnesium iodide prepared from 5.7 g. (0.04 mole) of methyl iodide and 1 g. (0.04 mole) of magnesium in 50 ml. of dry ether was added rapidly a solution of 7 g. (0.025 mole) of the *cis*-ketone II in 50 ml. of dry benzene. After heating under reflux for 2 hr. the reaction mixture was treated with aqueous ammonium chloride and worked up in the usual way (see the above procedure for the preparation of II). The crude product was recrystallized once from hexane (Skellysolve B) to give 5.3 g. (72%) of the *cis*-carbinol IV, m.p. 83–84°. Recrystallization of a sample once more for analysis raised the m.p. to 86–87°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.30; H, 8.59; N, 4.81.

In like manner from the *trans*-ketone III was obtained an 84% yield of the *trans*-carbinol V, m.p. 142–143° (from cyclohexane).

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.28; H, 8.54; N, 4.59.

Reaction of phenylmagnesium bromide with cocaine. Preparation of VII. To a stirred solution of 0.7 mole of phenylmagnesium bromide in 600 ml. of ether was added a solution of 0.088 mole of cocaine base (freed from 30 g. of the hydrochloride) in 500 ml. of dry ether. The mixture was stirred and heated under reflux for 18 hr. After cooling, a solution of 50 g. of ammonium chloride in 200 ml. of water was added dropwise to the stirred reaction mixture and the product was isolated in the usual way to give 15.4 g. (51%) of the glycol VII, m.p. 185–186° (from ethanol), $[\alpha]_D^{27}$ −23.5° (c = 0.04 g./ml.; $CHCl_3$), pK_a = 7.49 (by titration in aqueous methanol).

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.05; H, 7.79; N, 4.33. Found: C, 77.98; H, 7.72; N, 4.31.

The *quaternary methomethyl sulfate of* VII, m.p. 169–170°, was prepared by treating a sample of VII dissolved in methyl ethyl ketone with a slight excess of dimethyl sulfate, warming to about 40° for 1 hr., adding ether to the point of turbidity and cooling in an ice bath. The precipitated salt was recrystallized once from an isopropyl alcohol–ether mixture.

Anal. Calcd. for $C_{23}H_{31}NO_6S$: C, 61.45; H, 6.95; N, 3.12. Found: C, 60.90; H, 6.76; N, 3.06.

Dehydration of the glycol VII *to the diene* VIII. A mixture of 8.4 g. (0.026 mole) of the glycol VII, 18 ml. of concentrated hydrochloric acid, and 60 ml. of glacial acetic acid was heated under reflux for 2 hr. and then concentrated to dryness under reduced pressure. The residue was dissolved in water and made strongly alkaline with 40% aqueous sodium hydroxide. The precipitated oil was taken up in ether and dried over anhydrous sodium sulfate. Filtration and removal of the ether by distillation followed by two distillations of the residue under reduced pressure gave 4.5 g. of the diene VIII as a yellow oil, b.p. 201–203° (2.5 mm.), n_D^{25} 1.6338, $[\alpha]_D^{30}$ +548° (c = 0.04 g./ml.; $CHCl_3$), λ_{max} 282 mμ (ε = 17,800; 95% ethanol).

Anal. Calcd. for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 87.94; H, 7.59; N, 4.91.

The methiodide of VIII was prepared by dissolving 1 g. of the diene in 50 ml. of methyl ethyl ketone, heating to reflux for 2 min. with 2 g. of methyl iodide and allowing to stand for 2 days. Recrystallization of the crude product from ethanol gave 0.7 g. of *VIII methiodide*, m.p. 281–282° dec., $[\alpha]_D^{28}$ +450° (c = 0.004 g./ml.; H_2O).

Anal. Calcd. for $C_{22}H_{24}IN$: C, 61.54; H, 5.63; N, 3.26. Found: C, 61.57; H, 5.86; N, 2.97.

Methyl ester of anhydroecgonine IX. A mixture of 13 g. (0.0638 mole) of anhydroecgonine hydrochloride,[7] 6.5 g. of Amberlite XE-156 resin, 50 ml. of dry methanol, and 175 ml. of ethylene dichloride was stirred and heated under reflux for 21 hr. The cooled reaction mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. The residual glassy hydrochloride was treated with just enough saturated potassium carbonate solution to produce a fluid mixture which was then treated with solid anhydrous potassium carbonate to further salt out the somewhat water soluble base. The product was taken up in several portions of ether which were combined and dried over anhydrous sodium sulfate. Filtration, removal of the ether by distillation, and vacuum distillation of the residue gave 7.1 g. (62%) of IX, b.p. 124–126° (10 mm.) [Literature[7] reports b.p. 107° (7 mm.)], n_D^{25} 1.5006.

Addition of phenyllithium to IX. *Preparation of X.* A solution of phenyllithium was prepared by adding dropwise a solution of 42.4 g. (0.27 mole) of bromobenzene in 200 ml. of dry ether to a stirred suspension of 3.6 g. (0.52 mole) of lithium metal in 100 ml. of dry ether under an atmosphere of nitrogen. After stirring and heating under reflux for 2 hr., a solution of 8.1 g. (0.045 mole) of IX in 100 ml. of dry ether was added to the phenyllithium and the mixture was heated and stirred for 1 hr. longer. The cooled reaction mixture was then decomposed by the dropwise addition of 50 ml. of water and the solid which remained was collected by filtration. Two recrystallizations of the product from aqueous methanol gave 7.7 g. (56%) of the carbinol X, m.p. 209–210°, $[\alpha]_D^{29}$ −52.0° (c = 0.011 g./ml.; $CHCl_3$). The infrared spectrum of this material showed typical hydroxyl but no carbonyl absorption.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59; O, 5.24. Found: C, 82.37; H, 7.83; N, 4.57; O, 5.32.

Treatment of 1.5 g. of X with 0.6 g. of dimethyl sulfate in methanol gave, after two recrystallizations from dry ethanol, 1.1 g. of the *methomethyl sulfate of* X, m.p. 186–187°.

Anal. Calcd. for $C_{23}H_{29}NO_6S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 63.96; H, 6.86; N, 3.27.

Dehydration of the carbinol X *to the diene* VIII. A 1.5-g. sample of the carbinol X was treated with a solution of 4 ml. of concentrated hydrochloric acid in 12 ml. of glacial acetic acid exactly as described above for the dehydration of the glycol VII. The crude diene base was treated directly with methyl iodide in the usual manner to give 0.4 g. of *VIII methiodide*, m.p. 275–276° (dec.).

Anal. Calcd. for $C_{22}H_{24}IN$: C, 61.54; H, 5.63; N, 3.26. Found: C, 61.63; H, 5.87; N, 3.16.

A mixture of this material with the methiodide, m.p. 281–282° (dec.), prepared from the diene VIII obtained by dehydration of VII, melted at 276–278° (dec.). Further proof of identity of these two materials comes from the fact that their infrared spectra in chloroform solution were qualitatively identical and their specific rotations (c =

0.021 g./ml. in $CHCl_3$) differed by only 2% (+443° and +450°).

Reaction of the hydroxyketones XI *with phenylmagnesium bromide. Preparation of the glycols* XII. A solution of phenyl Grignard reagent in ether was prepared in the usual way from 28.3 g. (0.18 mole) of bromobenzene and 4.3 g. (0.18 mole) of magnesium. The ether was then replaced by dry benzene and the stirred refluxing reagent was treated rapidly with a hot solution of 10 g. (0.0585 mole) of XI[8] in dry benzene. The reaction mixture was then heated under reflux overnight, cooled, and decomposed with aqueous ammonium chloride. The glycols XII were isolated in the usual manner in the form of solid free bases.

From the α-form of XI, m.p. 130°,[8] was obtained 6.6 g. (45%) of the *α-glycol XII*, m.p. 177–178° (from ethyl acetate).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.61; O, 12.85. Found: C, 72.41; H, 9.17; N, 5.76; O, 12.54.

From the β-form of XI, m.p. 85–86°,[8] was obtained 1.6 g. (11%) of the *β-glycol XII*, m.p. 180–181° (dec.) (from ethyl acetate). A mixture of the α- and β-glycols melted at 155–160°.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.61; O, 12.85. Found: C, 72.55; H, 9.11; N, 5.63; O, 12.94.

An attempt to increase the yield of the β-glycol XII by using toluene in place of benzene in the Grignard reaction led to essentially the same results. In addition to the poorer yield of addition product obtained from the β-isomer, the lower reactivity of this form as compared to the α-isomer was further indicated by the fact that the initial stage of the Grignard reaction of the α-form was exothermic. The β-isomer showed no such evidence of spontaneous reaction.

Reaction of pilocarpine (XIII) *with phenylmagnesium bromide. Preparation of* XIV. To a solution of phenylmagnesium bromide in ether prepared in the usual way from 37.7 g. (0.24 mole) of bromobenzene and 5.75 g. (0.24 mole) of magnesium was added in portions, 15 g. (0.06 mole) of powdered pilocarpine hydrochloride.[12] The mixture was stirred and heated under reflux overnight and decomposed as usual with aqueous ammonium chloride solution. The free base, insoluble in ether, was collected by filtration and gave, after recrystallization from dry ethanol, 14.3 g. (65%) of the glycol XIV, m.p. 285–288° (dec.). One recrystallization from dimethylformamide gave analytically pure XIV, m.p. 291–293° (dec.) (literature[9] reports m.p. 290°).

Anal. Calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.68. Found: C, 75.85; H, 7.71; N, 7.50.

XIV *Hydrochloride*, m.p. 137–139° dec. was recrystallized from an isopropyl alcohol–ether mixture. The specific rotation, $[\alpha]_D^{27}$, of the hydrochloride was −145° (c = 0.008 g./ml.; H_2O) whereas the $[\alpha]_D^{18}$ of pilocarpine hydrochloride is reported to be +91° (c = 0.02 g./ml.; H_2O).

Anal. Calcd. for $C_{23}H_{29}ClN_2O_2$: C, 68.90; H, 7.29; N, 6.98. Found: C, 68.78; H, 7.73; N, 6.85.

Dehydration of XIV *to* XV. A solution of 3.6 g. of the glycol XIV in 30 ml. of glacial acetic acid containing 10 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The mixture was concentrated to dryness under reduced pressure, the residue was dissolved in water and the solution was made strongly alkaline with saturated aqueous potassium carbonate. The liberated base was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil which could not be crystallized. It was taken up in ether and treated with ethereal hydrogen chloride. Recrystallization of the resulting salt from an ethanol-ether mixture gave 2 g. of *XV hydrochloride*, m.p. 254–256°, $[\alpha]_D^{27}$ +156° (c = 0.01 g./ml.; H_2O).

Anal. Calcd. for $C_{23}H_{27}ClN_2O$: C, 72.14; H, 7.11; N, 7.32 Found: C, 72.10; H, 6.91; N, 7.40.

Reaction of imidazolecarboxylic esters with phenylmagnesium bromide. Preparation of the carbinol XX. A solution of approximately 54 g. (0.335 mole) of phenylmagnesium bromide in 300 ml. of ether was treated with 250 ml. of tetrahydrofuran and the ether was removed by distillation. To the hot Grignard solution was added 10 g. (0.065 mole) of powdered 4-carbethoxy-5-methylimidazole (XVII).[13] The mixture was stirred and refluxed for a few minutes and then about three-fourths of the solvent was removed under reduced pressure. To the cooled mixture, ether was added followed by excess of an aqueous ammonium chloride solution. The solid which remained undissolved was collected by filtration, the ether layer was separated and concentrated to dryness. The residual solid was combined with the original filter-cake and dissolved in excess aqueous hydrochloric acid. This solution was then made alkaline with aqueous potassium hydroxide and the liberated solid base [11.5 g., 67%, m.p. 182–184° (dec.)] was again collected by filtration. Several recrystallizations from isopropyl alcohol gave analytically pure carbinol XX, m.p. 186–187° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60; O, 6.06. Found: C, 77.11; H, 5.89; N, 10.63; O, 6.35.

Heating under reflux for 4 hr. a mixture of 1.5 g. of XX, methyl ethyl ketone, and excess methyl iodide gave, after recrystallization from an isopropyl alcohol–ether mixture, 0.8 g. of the quaternary methiodide salt of the *N*-methyl derivative of XX, m.p. 223–224° (dec.) (from dry ethanol).

Anal. Calcd. for $C_{19}H_{21}IN_2O$: C, 54.29; H, 5.04; N, 6.67. Found: C, 54.25; H, 5.35; N, 6.56.

In a manner similar to the above procedure, addition of phenylmagnesium bromide to 4-carbomethoxyimidazole (XVI)[14] gave the *carbinol XIX* in 81% yield, m.p. 173–174° (dec.).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20; O, 6.39. Found: C, 76.56; H, 5.68; N, 10.88; O, 6.71.

Likewise, reaction of 4-carbomethoxy-2-methylimidazole (XVIII)[15] with the phenyl Grignard reagent led to the carbinol XXI in 78% yield, m.p. 200–201° (dec.) (from dry ethanol).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60; O, 6.06. Found: C, 77.30; H, 6.29; N, 10.44; O, 6.14.

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