[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J.]

Stereoselective Syntheses of *d,l*-α- and β-Lycoranes[1]

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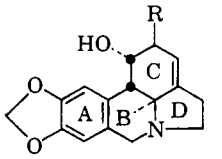
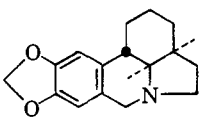
(±)-α-Lycorane (III) and β-lycorane (IV) have been synthesized, using Diels–Alder additions of 3,4-methylenedioxy-β-nitrostyrene to 1-substituted butadienes to construct the skeletons in a stereospecific manner. The syntheses confirm the configurations assigned to these bases, and consequently to the lycorine group of Amaryllidaceae alkaloids.

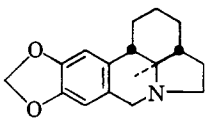
Lycorine, the most widespread and abundant alkaloid of the Amaryllidaceae, has been assigned the configuration shown in I on the basis of sound inferential arguments.[4,5] While syntheses of several aromatic degradation products of lycorine have been reported,[6] no derivative retaining any of the stereochemical problems of the parent has hitherto been synthesized. The present work was undertaken to investigate synthetic routes to the lycorine skeleton and with the concurrent aim of confirming the stereochemical assignment at the B/C ring junction, for which there is no direct evidence. The two stereoisomeric lycoranes, α- (III)[7] and β- (IV),[8] prepared from lycorine or its congener caranine (II) without skeletal isomerization, appeared to be the most suitable goals for this purpose. We now wish to report total syntheses of these two bases by methods which confirm the stereochemistry assigned to them and consequently the *trans* nature of the B/C junction in the lycorine group of alkaloids.



I, R = OH
II, R = H



III



IV

β-Lycorane.—A particularly attractive method for the construction of the octahydrophenanthridine moiety of III and IV begins with the Diels–Alder reaction with a β-nitrostyrene,[9] which has the advantage in this case of furnishing products of predictable stereochemistry.[10] In order to attach the five-membered ring D it was necessary to use a 1-substituted diene in the Diels–Alder addition. From the prolonged reaction of 3,4-methylenedioxy-β-nitrostyrene (V) with 1-acetoxybutadiene in refluxing toluene there was isolated a single adduct, m.p. 146–148°. Its structure and stereochemistry were assigned as shown in (VI) on the basis of the following arguments: (i) The fact that β-nitrostyrene and 2-ethoxybutadiene form an adduct in which the nitro and ethoxy groups have a 1,4-relationship[11] leads to the prediction, on polar or radical grounds, that a diene containing an electron-releasing group in the 1-position will yield, with the same dienophile, an adduct with the nitro group and 1-substituent in a 1,2-relationship.

(ii) The *trans* geometry of β-nitrostyrenes[12] is known to be preserved in their Diels–Alder adducts.[13]

(iii) The fact that the major product of the β-nitrostyrene–cyclopentadiene addition is the adduct with an *endo*-nitro group[13c,d] leads to the prediction that adducts of nitrostyrenes with 1-substituted acyclic dienes should have the nitro group *cis* to the diene substituent (Alder and Stein's rule[14] of "maximum accumulation of double bonds").

Further reactions of the adduct VI confirmed these conclusions. Catalytic hydrogenation over Raney nickel afforded as the predominant product a neutral solid, m.p. 188–190°, whose properties and infrared spectrum (2.91, 6.00 μ) revealed it to be the amide IX resulting from O–N acyl migration of the initially formed aminoester VII. A low yield of VII could be isolated as the hydrochloride from the mother liquors of IX; it had the expected ester absorption at 5.75 μ and was converted to IX by neutralizing the hydrochloride and warming. Both VII and IX gave the same O,N-diacetate VIII. The 1,2-relationship of the functional groups, strongly suggested by the facile rearrangement of the acetyl group, was proved conclusively by hydrolysis of IX to the aminoalcohol X, which consumed somewhat more than one equivalent of periodic acid.

(1) This work was generously supported by the Alfred P. Sloan Foundation and research grant RG-6568 from the Public Health Service, to whom the authors express their appreciation.

(2) Alfred P. Sloan Research Fellow.

(3) National Science Foundation Coöperative Fellow, 1959–1960.

(4) W. C. Wildman, in "The Alkaloids," Vol. VI, edited by R. H. F. Manske, Academic Press, Inc., New York, N. Y., 1960, p. 289.

(5) K. Takeda and K. Kotera, *Pharm. Bull. (Japan)*, **5**, 234 (1957); Y. Nakagawa and S. Uyeo, *J. Chem. Soc.*, 3736 (1959).

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(8) K. Kotera, *Tetrahedron*, **12**, 240 (1961).

(9) S. Sugasawa and K. Kodama, *Ber.*, **72**, 675 (1939); L. H. Mason and W. C. Wildman, *J. Am. Chem. Soc.*, **76**, 6194 (1954); W. C. Wildman and W. T. Norton, *ibid.*, **76**, 152 (1954).

(10) J. G. Martin and R. K. Hill, *Chem. Revs.*, **61**, 537 (1961).

(11) W. C. Wildman, R. B. Wildman, W. T. Norton and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1912 (1953).

(12) H. L. Goebel and H. H. Wenzke, *ibid.*, **60**, 697 (1938); V. N. Vasil'eva, V. V. Perekalin and V. G. Vasil'ev, *Zhur. Obschei Khim.*, **31**, 2171 (1961).

(13) (a) R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954); (b) W. E. Noland, H. I. Freeman and M. S. Baker, *ibid.*, **78**, 188 (1956); (c) G. I. Poos, J. Kleis, R. R. Wittekind and J. D. Rosenau, *J. Org. Chem.*, **26**, 4898 (1961); (d) J. Weinstock, N. Schwartz and M. F. Kormendy, *ibid.*, **26**, 5247 (1961).

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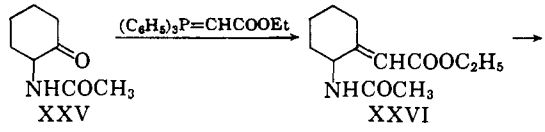
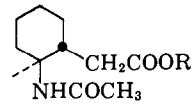
Oxidation of IX with chromic acid in pyridine gave the ketone XI in 81% yield. Of the condensation methods available for the attachment of the two carbons necessary to complete ring D, the Wittig reaction was chosen to preclude the possibility of forming an enamine derivative. Since the action of Wittig reagents on ketoamides had not been reported, the reaction was first tried on a close model. 2 - Acetamidocyclohexanone (XXV) reacted smoothly with carbethoxymethylenetriphenylphosphorane[15] to form the unsaturated ester XXVI in good yield. Hydrogenation with palladium in ethanol or with platinum in acetic acid gave the same dihydroester (XXVII), which was



XXV XXVI



XXVII, R = C_2H_5
XXVIII, R = H

hydrolyzed to the known[16] *trans*-2-acetamidocyclohexaneacetic acid (XXVIII).

Ketone XI was then subjected to the Wittig reaction under the same conditions. To separate the product XIII from the triphenylphosphine oxide formed required careful chromatography, and it proved simpler to saponify the total mixture and separate the acid XII by virtue of its alkali solubility. Some tentative information about the geometry of the double bond was obtained by refluxing the acid XII with acetic anhydride; the crude product had no O–H or N–H absorption in the infrared, but had bands at 5.78 and 5.84 μ characteristic of imides. The supposed imide XIV could not be obtained crystalline, however, and it was not possible to prove whether the carboxyl in XII had isomerized during the reaction.[17]

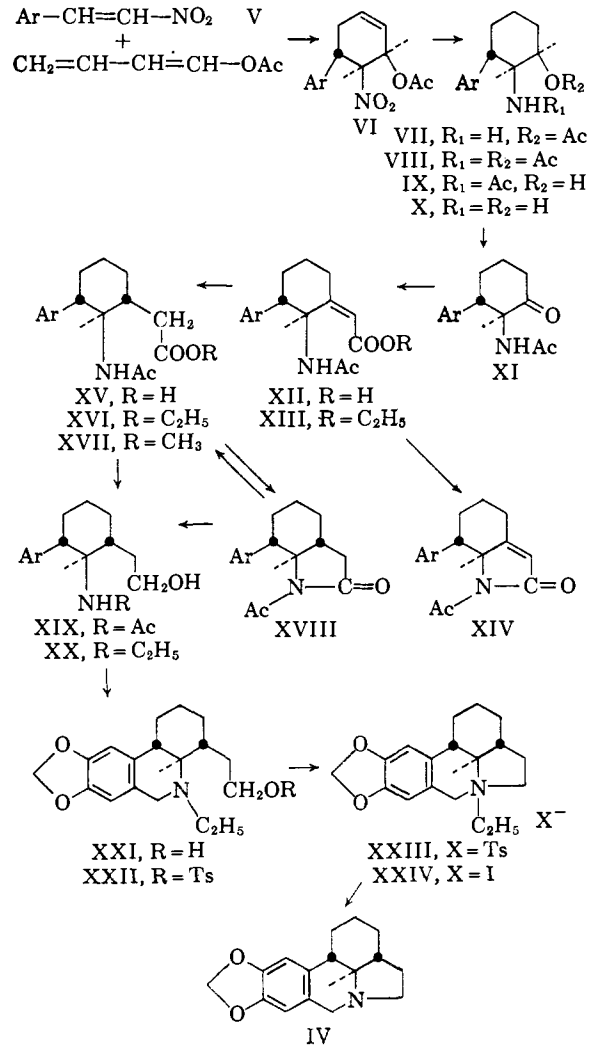
Hydrogenation of XIII using palladium–charcoal in ethanol or platinum in acetic acid led to the saturated ester XVI, which was hydrolyzed to the acid XV; the same acid resulted from hydrogenation of XII. On the reasonable assumption that the stereochemical course of these hydrogenations parallels that of the close relative XXV, the all-equatorial configuration shown is assigned to these products.

Attempts to remove the N-acetyl group from XVI were unsuccessful. Alkaline hydrolysis proceeded only as far as XV, while heating with hydrochloric acid caused decomposition. Warming with acetic anhydride converted XV to the imide XVIII, which on hydrolysis with either acid or alkali, however, only regenerated XV. Consequently, a slightly more circuitous route was chosen to complete the synthesis.

Lithium aluminum hydride reduction of the methyl ester XVII or of the imide XVIII gave the hydroxyamide XIX when carried out in ether at room temperature, but afforded the aminoalcohol XX when carried out in refluxing tetrahydrofuran. The product (XXI) of Pictet–Spengler ring closure with formaldehyde on XX could not be crystallized and was used without purification in the subsequent step. That condensation had occurred in the desired manner, however, was indicated by integration of the n.m.r. spectrum of XXI, which showed only two aromatic protons.

Treatment of XXI with one equivalent of *p*-toluenesulfonyl chloride in pyridine at room temperature and finally for a short while at 100° gave a 50% yield of an ether-soluble oil, which was not investigated further, and 40% of an amorphous, water-soluble quaternary tosylate (XXIII). The latter showed infrared bands characteristic of tosylate anion, and was converted to the corresponding crystalline iodide XXIV by treatment with aqueous potassium iodide.

Hofmann elimination appeared to be a reasonable method of removing the ethyl group of XXIV.



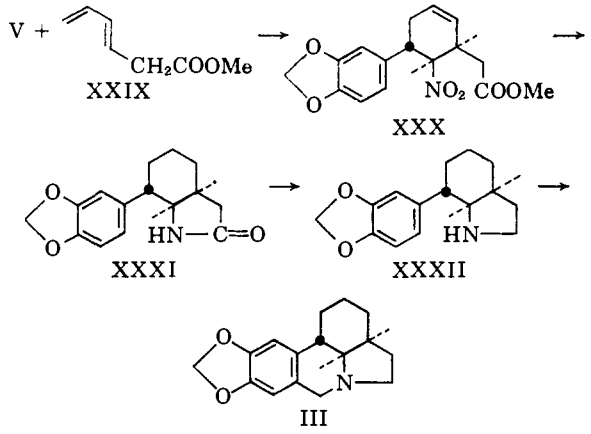
(15) Compare the difficulty reported by other workers in treating this Wittig reagent with ketones; S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961); *Chemistry & Industry*, 990 (1961).

(16) H. Booth and F. E. King, *J. Chem. Soc.*, 2688 (1958). We are greatly indebted to Dr. Booth for sending us a sample of this acid for comparison.

(17) For a discussion of the stereochemistry of the Wittig reaction see H. O. House and G. H. Rasmussen, *J. Org. Chem.*, **26**, 4278 (1961).

Of the hydrogens β to the nitrogen atom, the two in ring C have the wrong stereochemistry for the usual *trans-anti*-parallel elimination process, while the reluctance of those in ring D to participate is shown by the failure of dihydrolycorine methiodide to undergo Hofmann elimination.[18] In fact, conversion of the salt XXIV to the corresponding hydroxide and pyrolysis yielded (±)-β-lycorane (IV), m.p. 88°, whose infrared spectrum in carbon disulfide solution was completely identical with that of the authentic 1-base.[8,19] This synthesis consequently confirms the stereochemistry assigned to β-lycorane and provides unambiguous evidence for the *trans* B/C ring juncture in lycorine and its relatives.

α-Lycorane.—With the knowledge thus gained that the Diels–Alder addition of a β-nitrostyrene to a 1-substituted butadiene did yield an adduct of the predicted structure and stereochemistry, it became possible to design a neater and much shorter synthesis of the α-isomer of lycorane. The addition of 3,4-methylenedioxy-β-nitrostyrene to methyl hexa-3,5-dienoate (XXIX) gave moderate yields of the adduct XXX. Its structure and stereochemistry follow from the arguments presented earlier. Catalytic hydrogenation was accompanied by spontaneous ring closure to give the lactam XXXI. Completion of the skeleton followed readily by lithium aluminum hydride reduction to the amine XXXII and Pictet–Spengler closure. The product was identified as (±)-α-lycorane (III) by comparison of its infrared spectrum with that of an authentic sample prepared from lycorine.



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Experimental

3-Acetoxy-4-nitro-5-(3,4-methylenedioxyphenyl)-cyclohexene (VI).—A sealed Pyrex tube containing 20.0 g. of 3,4-methylenedioxy-β-nitrostyrene,[20] 42.4 g. of 1-acetoxybutadiene,[21] 0.15 g. of hydroquinone and 90 ml. of toluene was heated for 36 hr. in a bath of refluxing toluene. After cooling, the tube was opened and the solution concentrated to one-half its initial volume. The solid was collected and washed with ethanol; it proved to be nearly pure unreacted nitrostyrene. The filtrate was concentrated in stages and additional crops collected, which became progressively richer in the colorless adduct. Complete separation of the adduct from starting material was effected by repeated crystallization from benzene–ethanol. In five identical runs, an average of 6.0 g. of nitrostyrene was recovered, and an average yield of 5.78 g. (35%, based on unrecovered starting material) of pure adduct, m.p. 146–148°, was obtained.

Anal. Calcd. for $C_{15}H_{15}NO_6$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.02; H, 4.90; N, 4.56.

Larger runs were carried out more conveniently[22] by refluxing the reactants (in the same ratio) under dry nitrogen for 48 hr.; the yield of adduct, from 100 g. of the nitrostyrene, averaged 26 g.

2-Acetamido-3-(3,4-methylenedioxyphenyl)-cyclohexanol (IX).—To a solution of 10 g. of the adduct VI in 100 ml. of ethyl acetate and 50 ml. of ethanol, warmed to 50–60°, was added 3–4 tsp. of freshly prepared Raney nickel catalyst (W-2), and the mixture hydrogenated in a Parr shaker at 50 p.s.i. After 24 hr., the solution was filtered, concentrated and cooled to afford the fluffy white product. Dilution of the filtrate with ether gave an additional crop. From a total of 69 g. of VI was obtained 41.73 g. (67%) of the hydroxyamide, m.p. 185–190°. Two recrystallizations from ethanol raised the m.p. to 188–190°. The compound showed infrared absorption (in chloroform) at 2.9 μ (O–H) and 6.0 μ (amide).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.77; H, 6.99; N, 5.09.

The O,N-diacetate VIII was formed by refluxing 0.22 g. of IX with 5 ml. of acetic anhydride and 0.2 g. of sodium acetate for 3.5 hr. The mixture was stirred with 20 ml. each of water and chloroform, and the chloroform layer separated and concentrated. Trituration of the residue with methanol gave 0.11 g. of crystals, m.p. 195–202°. Recrystallization from methanol–hexane gave pure material, m.p. 200–202°, which showed infrared bands (in chloroform) at 2.9 μ (N–H), 5.77 μ ($OCOCH_3$) and 6.0 μ (amide).

Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.01; H, 6.60; N, 4.27.

2-Amino-3-(3,4-methylenedioxyphenyl)-cyclohexyl Acetate (VII).—In a run involving the hydrogenation of 26.3 g. of VI as described above, the mother liquors remaining after separation of the amide IX were evaporated, taken up in chloroform, and extracted with 0.1 *N* hydrochloric acid. The acidic extracts were evaporated to dryness at reduced pressure, and the sticky residue triturated with ethanol and ether, yielding 4.44 g. (6.2%) of the amine hydrochloride, m.p. 221–224°dec. Two recrystallizations from ethanol gave colorless needles, m.p. 228–230° dec.; infrared absorption (Nujol) at 5.75 μ ($OCOCH_3$).

Anal. Calcd. for $C_{18}H_{20}NO_4Cl$: C, 57.41; H, 6.42; N, 4.46. Found: C, 57.05; H, 6.42; N, 4.52.

Acetylation with acetic anhydride–sodium acetate gave the same diacetate as obtained from IX, m.p. and mixed m.p. 200–202°.

2-Amino-2-(3,4-methylenedioxyphenyl)-cyclohexanol (X).—A solution of 550 mg. of IX in 20 ml. of ethanol was heated on a steam-bath with 10 ml. of concentrated hydrochloric acid for 4 hr. under reflux. The alcohol was then boiled away and 20 ml. of water added. The acidic solution was filtered, washed with ether (2 × 20 ml.), made alkaline with potassium carbonate and extracted with ether (3 × 30 ml.). After drying over potassium carbonate and concentration, the ethereal extracts gave 400 mg. of partially crystalline material, which was crystallized from ether to give the amino-alcohol, m.p. 142–143°, infrared adsorption (in chloroform) at 3.1, 3.5–4.0 μ broad (N–H, O–H).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.23; N, 5.95. Found: C, 66.03; H, 7.23; N, 5.93.

Reaction of 2-Amino-3-(3,4-methylenedioxyphenyl)-cyclohexanol with Periodic Acid.—A solution of 190 mg

(18) H. Kondo and H. Katsura, *Ber.*, **72**, 2083 (1939).

(19) (a) We are indebted to Dr. K. Kotera, Shionogi and Co., Ltd., Osaka, Japan, for kindly sending us the infrared spectrum of (−)-β-lycorane. (b) A preliminary report of this synthesis has been published; R. K. Hill, J. A. Joule and L. J. Loeffler, *Chemistry & Industry* 1573 (1962).

(20) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

(21) O. Wichterle and M. Hudlický, *Coll. Czech. Chem. Commun.*, **12**, 564 (1947).

(22) The skilled technical assistance of S. Barcza and R. C. Siegel in carrying out these runs is gratefully acknowledged.

(0.81 mmole) of the amino-alcohol X in 20 ml. of freshly distilled dioxane was treated with 20 ml. of 0.1 *M* periodic acid and kept at room temperature for 24 hr. Excess potassium bicarbonate was added, then potassium iodide, and the liberated iodine titrated with thiosulfate in the usual way. With the correction for the dioxane blank, 0.972 mmole of periodate was found to have been consumed, or 1.2 moles per mole of amino-alcohol.

2-Acetamido-3-(3,4-methylenedioxyphenyl)-cyclohexanone (XI).—To a suspension of Sarett reagent, prepared from chromium trioxide (11.5 g.) and pyridine (300 ml.), 9.79 g. of IX in 250 ml. of pyridine was added at room temperature with stirring under nitrogen during 30 minutes. The mixture was stirred for a further 15 hr., diluted with 500 ml. of ethyl acetate, and filtered through short columns of Celite and alumina. The eluate and ethyl acetate washings (an additional 500 ml.) were evaporated to dryness under reduced pressure and the partially crystalline residue recrystallized from ether to afford 7.88 g. (81%) of the colorless ketone, m.p. 151–153°. A chloroform solution had infrared bands at 2.91, 3.0(sh.) μ (N–H), 5.81 μ (ketone) and 5.99 μ (amide).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.60; H, 6.20; N, 5.23.

2-Acetamido-3-(3,4-methylenedioxyphenyl)-cyclohexylideneacetic Acid (XII).—A solution of carbethoxymethylenetriphenylphosphorane[23] (6.87 g.) in 150 ml. of dry benzene was added dropwise, under nitrogen, to a refluxing solution of XI (5.37 g.) in 100 ml. of benzene over a period of 0.5 hr. After 12 hr. refluxing, the solvent was removed under reduced pressure, the residue taken up in 100 ml. of ethanol and heated on a steam-bath with 20 ml. of 25% sodium hydroxide for 4 hr. The alcohol was distilled and replaced by 100 ml. of water, and the cooled aqueous solution washed with ether. Acidification and extraction with ether gave 5.56 g. of the crude gummy acid; crystallization from benzene provided 3.47 g. (51.8%) of a benzene solvate of XII, m.p. 158–159°.

Anal. Calcd. for $C_{17}H_{19}NO_5 \cdot {}^1/_3C_6H_6$: C, 66.49; H, 6.12; N, 4.08. Found: C, 66.94; H, 6.30; N, 4.06.

The pure acid could be obtained by crystallization from ether–chloroform; m.p. 198–199°.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.36; H, 5.99; N, 4.42. Found: C, 64.67; H, 5.97; N, 4.39.

The ethyl ester XIII was obtained by omitting the alkaline hydrolysis in the above procedure. The residue from the Wittig reaction on 14.95 g. of XI, carried out as described above, was chromatographed over alumina in methylene chloride. The center fractions were recrystallized several times from benzene–hexane to afford 5.80 g. (31%) of the pure ester, m.p. 167–169°. The infrared spectrum (in chloroform) showed bands at 2.90 μ (N–H), 5.84 μ (conjugated ester), 5.95 μ (amide) and 6.04 μ (C=C).

Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.15; H, 6.72; N, 4.15.

Reaction of XII with Acetic Anhydride.—The acid XII (95 mg.) was refluxed with 3 ml. of acetic anhydride for 3 hr. The solvent was removed under reduced pressure and the residue partitioned between cold potassium carbonate solution and ether. The ether solution, after drying and concentration, furnished a yellow gum (60 mg.) which could not be induced to crystallize. Its solution in carbon tetrachloride showed no infrared absorption in the N–H, O–H region, but had bands at 5.78 and 5.84 μ (imide).

2-Acetamido-3-(3,4-methylenedioxyphenyl)-cyclohexylacetic Acid (XV).—A solution of 3.70 g. of the unsaturated acid XII in 100 ml. of ethanol was hydrogenated over Adams catalyst (0.3 g.) at atmospheric pressure. One mole of hydrogen was absorbed in 2.5 hr. The solution was filtered and taken to dryness under reduced pressure, and the resulting gum crystallized from chloroform to give 3.10 g. of the acid XV, m.p. 200–202°.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.73; H, 6.74; N, 4.37.

The ethyl ester XVI was prepared in 95% yield by hydrogenation of the ester XIII in ethanol over 10% palladium–charcoal at 50 p.s.i. in a Parr shaker. Recrystallized from methanol–hexane, it melted at 133–134°, and had infrared bands (in chloroform) at 2.91 μ (N–H), 5.80 μ (ester) and 5.99 μ (amide). Performing the hydrogenation with platinum in acetic acid gave the same product, m.p. and mixed m.p. 132–134°.

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.70; H, 7.22; N, 4.22.

Hydrolysis of XVI by refluxing an ethanolic solution with 50% aqueous potassium hydroxide for 57 hr. gave an 80% yield of the acid XV, m.p. 200–202°.

The methyl ester XVII was prepared by treating XV with an ethereal solution of diazomethane. Crystallized from ether, it melted at 148–149°.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.88; H, 7.03; N, 4.15.

N-Acetyl-7-(3,4-methylenedioxyphenyl)-hexahydrooxindole (XVIII).—A 300-mg. sample of the acid XV was heated under reflux in 2 ml. of acetic anhydride for 3.5 hr. The solvent was removed under reduced pressure and the residue distributed between ether and cold potassium carbonate solution. The ether solution, after drying and evaporating, left a pale yellow glass (280 mg.) which was crystallized from ether containing a little ethanol to afford the imide, m.p. 140–141°. The infrared spectrum (in chloroform) was devoid of absorption in the O–H and N–H region, but had the characteristic[24] imide bands at 5.75 and 5.83 μ.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.27; H, 6.48; N, 4.63.

Heating the imide XVIII with aqueous ethanolic alkali or with aqueous hydrochloric acid in dioxane regenerated the acid XV, m.p. and mixed m.p. 200–202°. Warming the imide with aqueous methanolic hydrochloric acid on a steam-bath for 1.5 hr. gave the methyl ester XVII, m.p. 148–149°.

N-Acetyl-2-(3,4-methylenedioxyphenyl)-6-(β-hydroxyethyl)-cyclohexylamine (XIX).—An ether solution of the ester XVII (230 mg.) was stirred with a 100% excess of lithium aluminum hydride for 3 hr. at room temperature. After the addition of enough water to hydrolyze excess reagent and salts, the suspension was filtered, and the filtrate dried and concentrated. Crystallization of the residue from ether gave 133 mg. of the amido-alcohol, m.p. 155–156°, with infrared absorption (in chloroform) at 2.92, 3.00 μ (O–H, N–H) and 6.02 μ (amide).

The same product, m.p. and mixed m.p. 155–156°, was obtained by reduction of the imide XVIII in exactly the same manner.

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.79; H, 7.77; N, 4.49.

N-Ethyl-2-(3,4-methylenedioxyphenyl)-6-(β-hydroxyethyl)-cyclohexylamine (XX).—A solution of 440 mg. of ester XVII in 40 ml. of tetrahydrofuran containing a molar excess of lithium aluminum hydride was refluxed for 5 hr. The solvent was removed under reduced pressure, the residue taken up in ether and worked up as in the preceding experiment. The hydroxyamine crystallized from a small volume of ether to give 234 mg. of product, m.p. 109–110°, with no carbonyl absorption in the infrared (in carbon tetrachloride solution).

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.80; H, 8.70; N, 4.78.

The same product was obtained by reduction of the imide XVIII under the same experimental conditions.

***d,l*-β-Lycorane Ethiodide (XXIV).**—A mixture of 284 mg. of the aminoalcohol XX, 2 ml. of 30% aqueous formaldehyde, 50 mg. of potassium bicarbonate and 5 ml. of methanol was heated on the steam-bath for 45 minutes, with replacement of the methanol as it evaporated. One ml. of 6 *N* hydrochloric acid was added and the mixture heated an additional 45 minutes. The solution was cooled and washed with ether, made alkaline with potassium carbonate, and extracted with ether. Evaporation of the dried extracts left 256 mg. of XXI as a colorless oil.

This oil was kept with 160 mg. of *p*-toluenesulfonyl chloride in 5 ml. pyridine for 15 hr. at room temperature, then warmed on the steam-bath for 45 minutes and the solvent removed under reduced pressure. The residue was distributed between aqueous potassium carbonate and ether, and the aqueous layer washed several times with

(23) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

(24) C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **84**, 565 (1962), report bands at 5.78 and 5.94 μ for N-acetylpyrrolidone.

ether. The combined ethereal extracts yielded a colorless oil (120 mg.) which was not investigated further. Extraction of the aqueous solution with chloroform yielded 130 mg. of the amorphous quaternary toluenesulfonate XXIII, which could not be crystallized. In chloroform solution, it showed infrared peaks at 8.57, 8.94, 9.70 and 9.90 μ characteristic of tosylate anion.[25]

A solution of 120 mg. of the amorphous tosylate in 2 ml. of hot water was treated with 100 mg. of potassium iodide. The resulting gum was scratched and cooled until it crystallized, affording 95 mg. of the quaternary iodide XXIV, m.p. 244–245°.

Anal. Calcd. for $C_{16}H_{28}NO_2I$: C, 52.30; H, 5.81; N, 3.44. Found: C, 52.13; H, 6.08; N, 3.18.

***d,l*-β-Lycorane (IV).**—An aqueous solution of the ethiodide XXIV was converted to the quaternary hydroxide by passing through a column of Dowex anion exchange resin, previously equilibrated with sodium hydroxide. The eluate and washings were concentrated under reduced pressure and the residue heated in an oil-bath at 170–210° at 1 mm. The colorless distillate was converted to its hydriodide, which, after recrystallization from ethanol, melted at 258–259°.

Anal. Calcd. for $C_{16}H_{19}NO_2 \cdot HI$: C, 49.88; H, 5.24; N, 3.64. Found: C, 50.09; H, 5.51; N, 3.56.

Regeneration of the base from the hydriodide by treatment with aqueous bicarbonate, and recrystallization twice from pentane, gave *d,l*-β-lycorane, m.p. 88°. The infrared spectrum in carbon disulfide solution was identical with that of the authentic *l*-base.[8]

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.88; H, 7.61; N, 5.49.

Methyl 5-(3,4-Methylenedioxyphenyl)-6-nitrocyclohex-2-enylacetate (XXX).—A mixture of 1.26 g. of methyl hexa-3,5-dienoate (XXIX),[26] 0.97 g. of 3,4-methylenedioxy-β-nitrostyrene, 0.1 g. of hydroquinone and 3 ml. of toluene was heated at 111° in an evacuated, sealed tube for 4 days. After cooling, unreacted nitrostyrene (300 mg.) was collected by filtration. Concentration of the filtrate to 1 ml. and cooling gave a further 0.03 g. of starting nitrostyrene. The residual solution was taken to dryness, dissolved in a little ether, and stored in the ice box until crystallization was complete. The product (330 mg., 31% based on unrecovered nitrostyrene) was recrystallized from ether to give the pure adduct, m.p. 117–118°. It showed infrared absorption (in carbon tetrachloride) at 5.74 μ (ester) and 6.47 μ (NO_2).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.27; H, 5.48; N, 4.45.

7-(3,4-Methylenedioxyphenyl)-hexahydrooxindole (XXXI).—The nitro function of the adduct XXX proved unusually resistant to reduction, as evidenced by the persistence of the infrared peak at 6.47 μ in the products of reduction under the following conditions: (i) hydrogenation over Adams catalyst in glacial acetic acid or in ethanol at room temperature and atmospheric pressure, (ii) hydrogenation over Raney nickel in ethanol at 50 p.s.i. and room temperature, (iii) hydrogenation over palladium–charcoal at 1000 p.s.i. and room temperature, (iv) reduction with 5% palladium–charcoal in refluxing cyclohexene for 18 hr.,[27] and (v) reduction with iron in refluxing acetic acid. Reduction was finally achieved as follows: a solution of 1.02 g. of the adduct XXX in 50 ml. of hot ethanol was hydrogenated over 0.5 g. of 5% palladium–charcoal in a steel bomb at 100° and 1000 p.s.i. for 6 hr.[28] The reaction mixture was filtered, the filtrate boiled to dryness, and the residual oil partitioned between ether (100 ml.) and 50 ml. of 2 *N* hydrochloric acid. The ethereal layer was dried over potassium carbonate and concentrated to provide 600 mg. of partly crystalline lactam. Recrystallized from ether, it melted at 191–192°.

Anal. Calcd. for $C_{18}H_{17}NO_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.58; H, 6.60; N, 5.23.

***d,l*-α-Lycorane (III).**—A solution of 500 mg. of the lactam XXXI in 20 ml. of tetrahydrofuran containing a molar excess of lithium aluminum hydride was refluxed for 18 hr. The cooled reaction mixture was treated with a small volume of water to destroy excess hydride and the solvent distilled. The residue was treated with 100 ml. of 3 *N* sodium hydroxide solution and extracted with six 50-ml. portions of ether. The combined ethereal extracts were dried over potassium carbonate and evaporated to dryness. The oily residue of XXXII (330 mg.) showed no carbonyl absorption in the infrared. It could not be induced to crystallize and was utilized without further purification in the final step.

A solution of the amine (330 mg.) in 15 ml. of methanol was heated with 200 mg. of potassium bicarbonate in 3 ml. of water and 4 ml. of 40% formalin on the steam-bath for 45 minutes. Concentrated hydrochloric acid (2 ml.) was added and the solution heated for a further 45 minutes. The methanol was boiled away, the residue cooled and washed with ether, then made alkaline with potassium carbonate and extracted with ether (3 × 20 ml.). After drying, the ether solution gave an oil (370 mg.) which was chromatographed on Merck alumina (20 g.). Benzene–hexane (24:1) eluted first an oil (82 mg.) and then crystalline material (150 mg.), which was recrystallized from hexane to give *d,l*-α-lycorane, m.p. 93–94°. The infrared spectrum (in carbon tetrachloride solution) of the racemic base was identical in all respects with that of genuine *l*-α-lycorane prepared by the method of Fales and Wildman.[7]

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.53; H, 7.45; N, 5.68.

2-Acetamidocyclohexanone (XXV).—A solution of 29.0 g. of 2-aminocyclohexanone hydrochloride[29] in 245 ml. of water was treated with 23.9 g. of anhydrous sodium acetate, followed by a solution of 29.6 ml. of acetic anhydride in 690 ml. of chloroform. The two-phase mixture was stirred vigorously for 3 hr., then kept at room temperature for 5 hr. Evaporation of the dried chloroform layer left a reddish-yellow liquid, which solidified rapidly when chilled. Recrystallization from petroleum ether (60–70°) yielded 16.4 g. (55%) of colorless needles, m.p. 93–95°, with infrared bands (in chloroform) at 2.94 μ (N–H), 5.82 μ (ketone) and 6.0 μ (amide).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.20; H, 8.47; N, 9.13.

Ethyl 2-Acetamido-cyclohexylideneacetate (XXVI).—To a refluxing solution of 10.4 g. of XXV in 200 ml. of dry benzene, under dry nitrogen, was added dropwise a solution of 23.2 g. of carbethoxymethylenetriphenylphosphorane in 250 ml. of benzene over a period of 1 hour. After stirring under reflux for 18 hr., the benzene was removed under reduced pressure, and the sticky solid residue triturated with two portions of ether (300 ml. and 100 ml.). The colorless residue (15.5 g.), m.p. 120–150°, was recrystallized twice from methanol–petroleum ether (60–70°), affording 9.12 g. (60%) of colorless needles, m.p. 161.5–163.5°. The infrared spectrum (in chloroform) showed bands at 2.91 μ (N—H), 5.85 μ (conjugated ester), 5.98 μ (amide) and 6.05 μ (C=C).

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.69; H, 8.50; N, 6.20.

Ethyl 2-Acetamido-cyclohexaneacetate (XXVII).—A solution of 6.0 g. of XXVI in 180 ml. of ethanol was hydrogenated over 1 g. of 10% palladium–charcoal in a Parr shaker at 50 p.s.i. for 3–4 hr. Removal of the ethanol under reduced pressure from the filtered solution, and recrystallization of the residue from methanol–petroleum ether (60–70°), gave 5.71 g. (94%) of fluffy colorless crystals, m.p. 101.5–103°. The infrared spectrum, in chloroform, showed absorption peaks at 2.91 μ (N–H), 5.81 μ (ester) and 6.0 μ (amide).

Hydrogenation of XXVI with platinum in acetic acid gave the same product, m.p. and mixed m.p. 101–103°, in 89% yield.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.17. Found: C, 63.28; H, 9.36; N, 6.16.

(25) F. L. Weisenborn and D. Burn, *J. Am. Chem. Soc.*, **75**, 259 (1953).

(26) G. P. Chiusoli, *Angew. Chem.*, **72**, 750 (1960). In the present work, the ester was prepared by diazomethane esterification of the acid, prepared by the method of R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 108 (1948).

(27) E. A. Braude, R. P. Linstead and K. R. H. Woolridge, *J. Chem. Soc.*, 3586 (1954).

(28) We are indebted to Dr. B. R. Franko of the Food Machinery and Chemical Corp., Princeton, N. J., for carrying out this hydrogenation.

(29) H. E. Baumgarten and J. M. Petersen, *J. Am. Chem. Soc.*, **82**, 460 (1960).

Attempted ethanolysis of XXVII to the corresponding aminoester, catalyzed by either dry hydrogen chloride or boron trifluoride, gave only starting material.

trans-2-Acetamidocyclohexaneacetic Acid (XXVIII).—Solutions of 3.1 g. of the ester XXVII in 50 ml. of ethanol and 21.45 g. of barium hydroxide octahydrate in 100 ml. of water were mixed and refluxed for 20 hr. under nitrogen. The mixture was cooled, diluted with 100 ml. of water, and carefully neutralized with 3.77 ml. of concentrated sulfuric acid in 60 ml. of water. After filtration of the precipitated barium sulfate, the filtrate was evaporated to dryness. The residue was taken up in 60 ml. of water, acidified to *p*H 4.1 with 0.1 *M* sulfuric acid, filtered, and again evaporated to dryness. The residue, m.p. 148–158°, was recrystallized twice from aqueous methanol, giving 0.94 g. of colorless needles, m.p. 181–183.5°. Mixed with an authentic sample of *trans*-2-acetamidocyclohexaneacetic acid,[18] m.p. 183–184°, it melted at 182.5–184°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.95; H, 8.60; N, 7.37.

Esterification of the acid with ethanol saturated with dry hydrogen chloride gave the original ester XXVII, m.p. 101–103°.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY, NASHVILLE 5, TENN.]

A Study of the Rates of Cyclization of Some *o*-Benzoylbenzoic Acids and of *o*-Phenoxybenzoic Acid in Polyphosphoric Acid[1]

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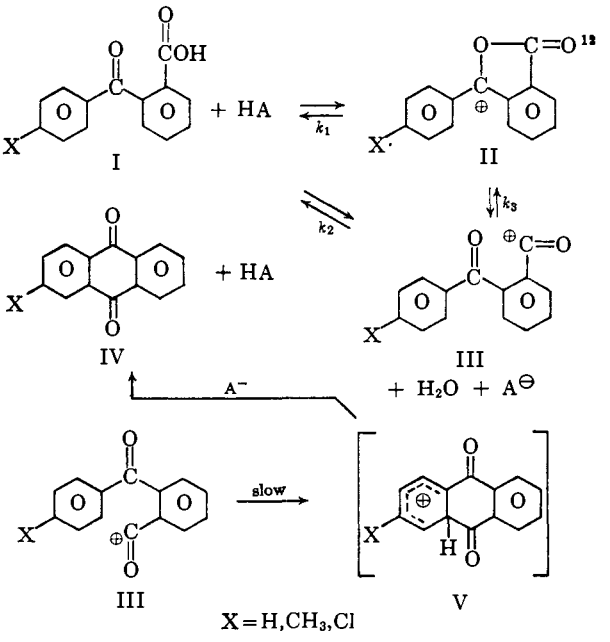
The rates of ring closure of *o*-benzoyl, *o*-(*p*-chlorobenzoyl)-, and *o*-(*p*-toluyl)-benzoic acids have been determined in polyphosphoric acids of various strengths. Maxima in the rate constants were found in the range 78–83% P_2O_5 content. On the other hand, the rate constants for the closely related ring closure of *o*-phenoxybenzoic acid in PPA did not show a maximum. All four reactions followed first-order kinetics. Explanations of a tentative nature are offered for the sake of provoking interest in this kinetic phenomenon.

The most frequently reported use of polyphosphoric acid (PPA) is cyclodehydration or, more specifically, intramolecular acylation.[4,5] A kinetic study of this type of reaction therefore seemed of practical as well as theoretical interest. Furthermore, earlier studies on the Beckmann rearrangement of acetophenone oximes[6] and on the decomposition of formic acid[7] showed that the rate constants either leveled off or passed through a maximum in increasingly concentrated PPA. It seemed of interest to see if this phenomenon was more general and occurred in other reactions.

To our knowledge only four kinetic studies have been carried out in PPA. Two have been described,[6,7] and two have been concerned with the subject of this paper, intramolecular acylation. Denny and Klemcluk[8] concluded that there was a small deuterium isotope effect in the ring closure of 2-deuterio-2′-carboxybiphenyl to fluorenone. Goldberg and Wragg[9] gave rate constants for the cyclization of *o*-phenoxybenzoic acid to xanthone in PPA of 81.6% P_2O_5 content. On re-examination of this reaction in this Laboratory, we found that the rate constants of reference 9 were too small by a factor of about 1000 and probably represented the rates of solution of the *o*-phenoxybenzoic acid in PPA rather than its rates of cyclization. Neither of these acylation studies was concerned with effects of changing the concentration of the medium on the reaction rates.

Since there are many similarities in acylation reactions in PPA and sulfuric acid, mechanism studies in sulfuric acid furnish an important basis for comparisons with the work reported here. Newman and co-workers[10,11] have shown that the intramolecular acylation of *o*-benzoylbenzoic acid to anthraquinone (X = H) in sulfuric acid may be represented by the following equations which will serve also for discussion of the mechanism in PPA.



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