of the compounds prepared are stated in Table I. Previously reported compounds are noted therein.

Experimental

α-(*p*-Ethylbenzenesulfonamido)-isocaproic Acid.—A solution of 7.72 g. (0.038 mole) of *p*-ethylbenzenesulfonyl chloride, prepared as described elsewhere,[3] in 25 ml. of acetone was added slowly from a separatory funnel to a mechanically stirred solution of 5.0 g. (0.038 mole) of L-leucine in 55 ml. of 2 *N* sodium hydroxide and 25 ml. of acetone. During the addition the mixture was cooled in an ice-bath. Water was added to dissolve the precipitated sodium chloride. The acetone was removed under vacuum at 60° and the cooled solution was acidified to thymol blue with concd. hydrochloric acid. The precipitated crystals were collected and dried. The yield of crude material was 5.48 g. or 48% of the theoretical amount. Recrystallization from hot water gave crystals, m.p. 117–118°, used in the analyses.

α-(*p*-Ethylbenzenesulfonamido)-isocapramide.—Three grams (0.01 mole) of the acid as prepared above was dissolved in 10 ml. of purified thionyl chloride and heated on a steam-bath to solution. The gaseous products and excess thionyl chloride were removed under vacuum leaving a viscous liquid. Excess concd. ammonium hydroxide was added to this liquid. The crude reaction mixture was treated with 200 ml. of water. The crystals were collected and dried. The yield was 1.96 g. or 65% of the theoretical amount. Recrystallization from 95% ethanol gave crystals, m.p. 202–203°, used in the analysis.

Acknowledgment.—The authors are indebted to the Research Committee of the College of Arts and Sciences of the University of Louisville for a grant in support of this work.

(3) R. H. Wiley and R. P. Davis, THIS JOURNAL, **74**, 6142 (1952).

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Improved Preparation of Stachyose

BY M. L. WOLFROM, R. C. BURRELL, A. THOMPSON[1] AND S. S. FURST

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The tetrasaccharide stachyose was first isolated by von Planta and Schulze[2] from the root sap of *Stachys tuberifera*. Although stachyose has been found in a number of other plants, the tuber of *Stachys tuberifera* is still one of the better sources of this sugar. The method of isolation has been modified by Tanret.[3]

We wish to report herein a simple procedure for obtaining stachyose from the tuber of *Stachys tuberifera* wherein the organic solids in the extract of the tuber were adsorbed on a column of carbon and removed selectively by washing with increasing strengths of ethanol, according to the general adaptation of Whistler and Durso.[4] From the eluates the sugar could readily be crystallized.

Experimental

Fresh tubers of *Stachys tuberifera* (1 kg.) were ground in a food chopper and were refluxed on a water-bath with 1750 ml. of 85% ethanol for 80 min. in the presence of 2.5 g. of precipitated calcium carbonate. The liquid was removed by filtration and the extraction was repeated with 500 ml. of 75% ethanol for 60 min. The extract was filtered and combined with the first filtrate to produce a clear brownish solution which was concentrated under reduced pressure to a sirup; yield 80 g. The sirup was dissolved in 1000 ml. of water and placed on a 290 × 105 mm. (i.d.) column of Darco G-60[5]:Celite[6] (1:1 by wt.) and washed with 10 l. of water. This solution was evaporated under reduced pressure to a sirup which failed to crystallize; yield 17 g. The column was then washed with 10 l. of 5% ethanol. Upon evaporation under reduced pressure, this solution yielded a sirup (13 g.) which was crystallized by dissolving in the minimum amount of warm water, cooling to room temperature, adding ethanol (95%) to incipient crystallization and allowing to stand at room temperature. The column was again washed with 10 l. of 10% ethanol. Upon evaporation this solution yielded 35 g. of sirup which crystallized from water–ethanol as described above. A further yield of sirupy material was obtained by washing the column with 10 l. of 20% ethanol. The sirup from this fraction showed only a slight tendency to crystallize. This residue was combined with the mother liquors from the 5 and 10% ethanol washings and evaporated to a sirup which was extracted with 500 ml. of boiling 85% ethanol to yield a further amount of 6 g. of crystals. The combined crystalline material was recrystallized from water by the addition of ethanol; yield of recrystallized material 39 g., m.p. 101–105° (sealed tube), $[\alpha]^{23}D$ +131.3° (*c* 4.5, water). These constants are in good agreement with those given in the literature for stachyose tetrahydrate.[3]

(1) Corn Industries Research Foundation Associate.

(2) A. von Planta and E. Schulze, *Ber.*, **23**, 1692 (1890).

(3) G. Tanret, *Bull. soc. chim.*, [4] **13**, 176 (1913).

(4) R. L. Whistler and D. F. Durso, THIS JOURNAL, **72**, 677 (1950).

(5) Decolorizing carbon; a product of Darco Department, Atlas Powder Co., New York, N. Y.

(6) No. 535, a siliceous filter-aid produced by Johns-Manville Co. New York, N. Y.

DEPARTMENTS OF CHEMISTRY AND OF AGRICULTURAL BIOCHEMISTRY
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The Reaction of Phosphorus Pentachloride with Epimeric 2-Aminocycloalkanol Hydrochlorides

BY EUGENE E. VAN TAMELEN AND RICHARD S. WILSON[1]

RECEIVED AUGUST 7, 1952

During the course of work being carried out in this Laboratory, it became desirable to investigate the synthesis of diastereoisomeric 2-chlorocycloalkylamines through the reaction of phosphorus pentachloride with *cis*- and *trans*-2-aminocycloalkanol hydrochlorides. The results of these studies, together with evidence for the stereochemistry of the products, are presented below.

The synthesis of a 2-chlorocyclohexylamine hydrochloride (IIa) from *trans*-2-aminocyclohexanol hydrochloride (Ia) by this route was first reported by Osterberg and Kendall.[2] Direct evidence for the *cis* configuration (and therefore displacement by phosphorus pentachloride with inversion) has been presented by Carter, *et al.*,[3] and, more recently, by Paris and Fanta.[4] The isomeric 2-chlorocyclohexylamine and derivatives have been obtained by several methods.[4–7] Attempts to obtain this *trans* isomer through the action of phosphorus pentachloride on the hydrochloride of *cis*-2-aminocyclohexa-

(1) Abstracted from a research report submitted by Richard S. Wilson in partial fulfillment of the requirements for the Master of Science degree, University of Wisconsin, February, 1952.

(2) A. E. Osterberg and E. C. Kendall, THIS JOURNAL, **42**, 2616 (1920).

(3) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *ibid.*, **71**, 637 (1949).

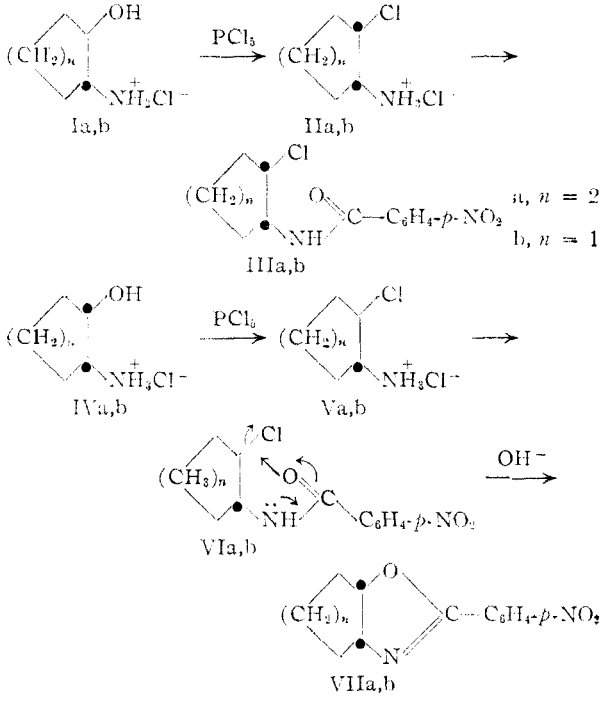
(4) O. E. Paris and P. E. Fanta, *ibid.*, **74**, 3007 (1952).

(5) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); **71**, 637 (1949).

(6) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950).

(7) T. L. Cairns, P. J. Graham, P. L. Barrick and R. S. Schreiber, *J. Org. Chem.*, **17**, 751 (1952).

nol[5] (IVa) failed; only dark-colored resins could be isolated. We have, however, been able to supplement the evidence for the stereochemistry of the two 2-chlorocyclohexylamines. The *p*-nitrobenzamide[5] (VIa) of the *trans* isomer was converted, although in poor yield, to the oxazoline[5] (VIIa) by brief heating in alcoholic sodium hydroxide solution; the *p*-nitrobenzamide[8] (IIIa) of the *cis* isomer, on the other hand, was recovered after similar treatment. These results are consistent with the established concept[9] of an internal displacement (of halogen) with inversion; only the *trans*-chloroamide is favorably oriented for such a process.



Parallel reactions in the cyclopentane series were attended by more success. *trans*-2-Aminocyclopentanol hydrochloride (Ib) was smoothly converted in 83% yield to *cis*-2-chlorocyclopentylamine (IIb); similarly, the *cis*-aminoalcohol[5] (IVb) afforded *trans*-2-chlorocyclopentylamine (Vb), although in poorer yield. Again, the structures of these products were established by treatment of their N-(*p*-nitrobenzoyl) derivatives (IIIb and VIb) with strong base. The *cis*-amide, after being heated to 70° for one minute with ethanolic sodium hydroxide, was recovered unchanged; longer reaction times gave only black, unpromising mixtures. The *trans*-amide (VIb), on the other hand, can be transformed with ease under identical conditions to *cis*-2-*p*-nitrophenyl-4,5-trimethyleneoxazoline[5,10] (VIIb). The amide VIb was identical with the N-(*p*-nitrobenzoyl)-2-chlorocyclopentylamine obtained by the rearrangement of *cis*-2-aminocyclopentyl *p*-nitrobenzoate hydrochloride.[10]

Thus the well-defined differences in reactivity between *cis*- and *trans*-2-chloroamides establish their configurations, which in turn indicate that the reaction of phosphorus pentachloride with both *cis*- and *trans*-2-aminocycloalkanols proceeds *with* inversion.

An interesting feature of *trans*-N-(*p*-nitrobenzoyl)-2-chlorocyclohexylamine (VIa) is its predominant hydrolysis, upon prolonged treatment with base, to *p*-nitrobenzoic acid and (presumably) *trans*-2-chlorocyclohexylamine, rather than ring closure to the oxazoline. The latter reaction appears to be exclusive in the cyclopentane series, but proceeds only to the extent of 3.5% with VIa. Molecular models show that the amide VIb is decidedly better oriented for ring closure than is VIa.

Experimental[11]

Ring-closure of *trans*-N-(*p*-nitrobenzoyl)-2-chlorocyclohexylamine (VIa).—To 1.10 g. of *trans*-N-(*p*-nitrobenzoyl)-2-chlorocyclohexylamine[5] (VIa) dissolved in 20 ml. of ethanol at 70°, was added with stirring 8.0 ml. of 1.09 *N* sodium hydroxide in 80% ethanol at 70°. The resulting solution was kept at 70° for three minutes and then poured into 10 ml. of water at 0°. The white precipitate (A) that formed was collected by filtration and dried. Recrystallization from 80% ethanol gave 0.13 g. (12%) of starting material, m.p. 177–180°. The filtrate from (A) deposited a small amount of precipitate on standing, which was filtered off with suction. This solid (B) was a mixture and was extracted with dilute hydrochloric acid to remove oxazoline. The extract, upon treatment with excess, dilute sodium hydroxide, yielded a white precipitate which melted at 108–114°. A single recrystallization from ethanol gave 30 mg. (3.5%) of 2-*p*-nitrophenyl-4,5-tetramethyleneoxazoline, m.p. 116.5–118.5°. A mixed melting point with authentic material[5] was undepressed. The filtrate from (B) was acidified with dilute hydrochloric acid. The precipitated material (m.p. 236–239°) was identified as *p*-nitrobenzoic acid by a mixed melting point determination. The yield in the present experiment (15%) could be raised considerably by longer treatment of the chlorocyclohexylamide with base.

Similar treatment of the corresponding *cis*-2-chloroamide IIIa[8] resulted only in the recovery of starting material. Refluxing with dilute base for 30 minutes resulted in considerable darkening, and again the only material isolated in a relatively pure state was starting amide.

***cis*-2-Chlorocyclopentylamine Hydrochloride (IIb).**—To 6.0 g. of *trans*-2-aminocyclopentanol hydrochloride[5] in a 500-ml. flask surrounded by an ice-bath was added 11.0 g. of phosphorus pentachloride dissolved in 100 ml. of dry benzene at 0°. The contents were stirred for 30 minutes. Then the viscous mixture was filtered by suction, and the precipitate was washed several times with dry carbon tetrachloride. Five and six-tenths grams (83%) of the chlorocyclopentylamine salt (m.p. 162–167°) was obtained. Recrystallization from dry benzene–absolute ethanol raised the melting point to 168.0–170.5°.

The free base was not isolated, but converted to the solid N-(*p*-nitrobenzoyl) derivative IIIb. Crystallization from 80% ethanol afforded colorless needles, m.p. 160.5–162.0°.

Anal. Calcd. for $C_{12}H_{13}N_2O_3Cl$: C, 53.64; H, 4.88. Found: C, 53.52; H, 4.80.

***trans*-2-Chlorocyclopentylamine Hydrochloride (VIb).**—*cis*-2-Aminocyclopentanol hydrochloride[5] (2.65 g.) was placed in a 500-ml. flask, and a solution of 5.0 g. of phosphorus pentachloride in dry benzene at 0° was added. The resulting mixture was stirred at room temperature for six hours. The suspended crystals were filtered and then washed several times with dry carbon tetrachloride. After drying thoroughly, the product melted at 209–212° and weighed 1.15 g. (39%). The analytical sample (m.p. 212.5–214.0°) was obtained by one recrystallization from dry benzene–absolute ethanol.

Anal. Calcd. for $C_5H_{11}NCl_2$: C, 38.48; H, 7.10. Found: C, 38.38; H, 6.84.

The chloroamine hydrochloride was converted to the N-(*p*-nitrobenzoyl) derivative in the usual fashion (to prevent ring closure of the product to the oxazoline, exactly two moles of base were added carefully to the aqueous solution

(8) M. T. Leffler and R. Adams, THIS JOURNAL, **59**, 2252 (1937).
(9) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).
(10) R. K. van Tamelen, *ibid.*, **74**, 2074 (1952).
(11) All melting points are corrected.

of the hydrochloride with shaking after each addition). The crude amide (m.p. 126–128°) was recrystallized once from dry benzene and then melted at 126.5–128.5°. No depression in melting point was observed on admixture with *trans*-N-(*p*-nitrobenzoyl)-2-chlorocyclopentylamine.[10] As a further check on its identity, the *p*-nitrobenzamide was converted, in 92% yield, to *cis*-2-*p*-nitrophenyl-4,5-trimethyleneoxazoline.[5]

Similar attempts at ring closure using the *cis*-*p*-nitrobenzamide (IIIb) led invariably to recovery of starting material.

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Mannich Bases Derived from α-Phenoxyacetophenones

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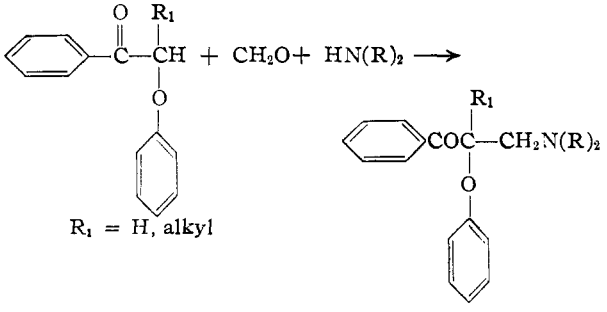
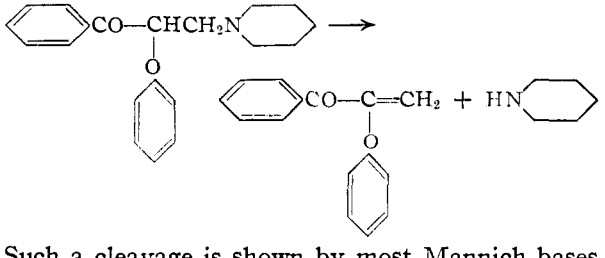
We have found that α-phenoxyacetophenones readily undergo the Mannich reaction. A survey of the literature[1,2] indicated that substituted acetophenones of this type have not been used in this reaction. The compounds used in the present work were α-phenoxyacetophenone, various ring-substituted α-phenoxyacetophenones and α-phenoxypropiophenone. The general reaction may be depicted as



The reactions were carried out by heating the ketone under reflux either with the amine hydrochloride and paraformaldehyde in the presence of a small amount of concentrated hydrochloric acid (procedure A) or with the amine and formaldehyde solution (procedure B). The compounds prepared are listed in Table I.

Attempted purification by distillation under reduced pressure of the Mannich base formed by the reaction of piperidine, α-phenoxyacetophenone and formaldehyde caused the elimination of piperidine with the resulting olefin being the only product which could be isolated.



Such a cleavage is shown by most Mannich bases when subjected to heat or distillation.[1,3]

(1) *Cf.* F. F. Blicke in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 303.

(2) H. Karbe, *Arch. Pharm.*, **283**, 48 (1950).

(3) J. H. Burckhalter and R. C. Fuson, THIS JOURNAL, **70**, 4184 (1948).

The first two amino ketones listed in Table I were reduced to the corresponding carbinols by catalytic reduction using palladium-on-charcoal as a catalyst. In each case only one diastereoisomeric form was isolated.

Experimental[4]

α-Phenoxy-*p*-(*n*-propoxy)-acetophenone.—To a stirred solution of 25.95 g. of *p*-(*n*-propoxy)-acetophenone in 100 ml. of ether at 10–15° was added dropwise 23.3 g. of bromine. After a short time a large amount of solid separated. The ether was removed *in vacuo* and a solution of 14.1 g. of phenol and 7.05 g. of sodium hydroxide in 70 ml. of water was added to the residue. The mixture was stirred and heated under reflux for 14 hours and, when cool, was extracted with ether. The ethereal extracts were washed with water, the ether removed by distillation and the residue was distilled *in vacuo* through a short Vigreux column; yield 19.1 g. (49%), b.p. 180–190° (0.6 mm.). The distillate solidified upon standing. Recrystallization from cyclohexane–petroleum ether gave colorless platelets melting at 49–50.5°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.57; H, 6.42.

α-(*p*-*n*-Propoxyphenoxy)-acetophenone.—A mixture of 19.9 g. (0.10 mole) of phenacyl bromide, 15.2 g. (0.10 mole) of *p*-*n*-propoxyphenol, 18.5 g. of anhydrous potassium carbonate and 200 ml. of acetone was heated under reflux with continuous stirring for 7 hours. The reaction mixture was cooled and then diluted with 200 ml. of water. The aqueous acetone mixture was extracted with ether. The ethereal solution after washing twice with 100-ml. portions of 10% sodium hydroxide was dried over sodium sulfate and then concentrated. The residual oil was crystallized from 2:1 ethyl alcohol–water. The cream-colored crystalline material was purified by recrystallization from 100 ml. of ethyl alcohol. The product was collected as colorless needles melting at 56.5–58°, wt. 22.5 g. (83%).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.89, 75.44; H, 7.06, 6.78.

α-(*p*-Chlorophenoxy)-acetophenone was prepared by the method described above for α-(*p*-*n*-propoxyphenoxy)-acetophenone using the corresponding amount of *p*-chlorophenol. The yield of crude product, melting at 96–97.5°, was 90%. Recrystallization from 3-A alcohol[5] gave large glistening plates melting at 98–99°.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.50; Cl, 14.37. Found: C, 68.25; H, 4.57; Cl, 14.66.

β-(Diethylamino)-α-phenoxypropiophenone Hydrochloride (Procedure A).—The procedure used was essentially that of Mannich and Lammering.[6] A mixture of 2.19 g. (0.02 mole) of diethylamine hydrochloride, 1 drop of concentrated hydrochloric acid, 0.9 g. (0.03 mole) of paraformaldehyde, 4.24 g. (0.02 mole) of α-phenoxyacetophenone[7] and 6 ml. of absolute ethanol was heated under reflux on a steam-bath. After a short time a homogeneous solution was obtained and refluxing was continued for 1 hour. Two additional 0.6-g. (0.02 mole) portions of paraformaldehyde were added and refluxing continued for an additional 2 hours after each portion had been added. After standing overnight the yellow solution was poured into 30 ml. of water and the resulting mixture extracted with ether and the ether extracts discarded. The aqueous layer was made alkaline with ammonium hydroxide and the resulting mixture extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and the hydrochloride prepared by the addition of an ethereal hydrogen chloride solution. The yield was 4.50 g. (68%), m.p. 128–129°. One recrystallization from methyl ethyl ketone–ethyl acetate (1:1) gave material melting at 128.5–129°.

β-(Dimethylamino)-α-(*p*-*n*-propoxyphenoxy)-propiophenone Hydrochloride (Procedure B).—Ten milliliters of 37% formaldehyde solution was added dropwise at 0° to a well-stirred solution of dimethylamine (slight excess) in 150 ml. of

(4) All melting points are corrected for stem exposure, unless otherwise indicated.

(5) Commercially denatured ethanol containing 5% methanol.

(6) C. Mannich and D. Lammering, *Ber.*, **55**, 3510 (1922).

(7) R. Mohlau, *ibid.*, **15**, 2498 (1882).