by treatment similar to that described for L-alanine, except that in the cases of isoleucine, leucine, methionine and valine, twice the volume of water and of buffer solution was employed. Each of the isomers except proline and serine was readily crystallized from water–ethanol in white, pure condition. L-Proline and L-serine come off the Dowex-1 resin (in hydroxyl or acetate form) in a highly colored state. Further treatment with the Dowex-1 resin removed some but not all of the colored impurity. Proline was dissolved in hot absolute ethanol, whilst serine was dissolved in hot water and treated with hot ethanol to 85%; on cooling to room temperature each solution deposited a small amount of a highly colored oil, leaving the supernatant solution clear and colorless. The supernatant solutions were each decanted from the oil and chilled at 0° for 1–2 days, whereby pure, colorless crystals of L-proline and of L-serine separated. Repetition of the preparation of these two isomers in the presence of 0.01 *M* KCN led to the isolation of L-serine and of L-proline in yield and state of purity reported in Table II.

L-Phenylalanine.—The racemic phenylalanine was subjected to oxidation in the same manner as that described for L-isoleucine but with the addition of KCN to 0.01 *M* final concentration to each reaction mixture. The product obtained after a 24-hour period of incubation when the oxygen consumption was apparently at an end was examined for optical purity[3] and revealed the presence of approximately 5% of the D-isomer. (If cyanide is omitted from the reaction mixture, the product at this stage contains about 20% of the D-form.) It was subjected to reoxidation in twice the volume of water and buffer as before, with twice the amount of enzyme, and once more in the presence of 0.01 *M* cyanide. After a further 24-hour period of oxidation at 37°, the isolated product after crystallization from water–ethanol was analytically and optically pure (Table II). In the case of DL-tyrosine oxidized by D-amino acid oxidase in the presence or absence of cyanide, the product in either case contained about 30% of the D-isomer; reoxidation in the presence of 0.01 *M* cyanide yielded a product still grossly contaminated with the D-form. A quite similar situation appeared to hold in the case of DL-tryptophan. It appeared probable that in these cases the lower fatty acid was about as inhibitory as the α-keto acid, and attempts to prepare the L-isomers of tyrosine and of tryptophan by the present procedures were therefore abandoned.

L-Hydroxyproline.—DL-Hydroxyproline is not readily available, and to test the present procedure for the preparation of the L-isomer, a suitable substrate was obtained by the epimerization of L-hydroxyproline in hot baryta solution. Leuchs and Geiger[14] prepared the epimeric mixture of L-hydroxyproline and D-allohydroxyproline (app. 1:1) in this manner, isolating the mixture after quantitative removal of barium ion with sulfate. Their procedure was modified to the extent of heating a solution of 20 g. of L-hydroxyproline in 250 ml. of water containing 150 g. of crystalline baryta at 120° for 24 hours, diluting with water and removing excess barium ion with CO_2 gas, and pouring the filtrate on a Dowex-50 resin (H^+) column, followed by a water wash. This was followed by 1 *N* NH_4OH until the ninhydrin reaction was negative, the eluate was evaporated to dryness to remove ammonia, and the crystalline, ammonia-free residue dried; yield 95%, $[\alpha]^{25}D$ −6.4° (*c* 2, H_2O).[24]

The epimeric mixture was subjected to oxidation for 24 hours as described above for L-alanine, with the amount of enzyme given in Table I, and in the presence of 0.005 *M* potassium cyanide. The L-isomer was isolated in the usual way and, after crystallization from water in the presence of excess ethanol, was found to be analytically and optically pure (Table II).

Preparation of L- and D-Methionine from 1 Mmole of DL-Methionine.—The oxidation of 149 mg. of DL-methionine was conducted in a 125-ml. Warburg vessel in the presence of one-tenth the volume of solvents, buffers, and amount of respective enzymes described above for the larger preparations. At the end of the oxidative reaction, the dialysis step was undertaken as above and the combined dialysates from either the L- or D-amino acid oxidase reaction treated successively on Dowex-50 and Dowex-1 resin columns as described above for D-leucine. The yield of D-methionine was 69.6 mg. (93%) and of L-methionine 63.0 mg. (85%).

(24) L-Allohydroxyproline treated in the same way yielded an epimeric mixture (app. 1:1) of L-allohydroxyproline and D-hydroxyproline with $[\alpha]^{25}D$ +7.4° (*c* 2, H_2O).

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Cleavage of 3-Tropanyl Chloride with Potassium Cyanide[1]

BY S. ARCHER, T. R. LEWIS AND BERNARD ZENITZ

RECEIVED AUGUST 30, 1957

The tropanyl chloride derived from tropine and thionyl chloride reacted with potassium cyanide in aqueous alcoholic solution to give a mixture of 2-allyl-5-cyano-1-methylpyrrolidines. The same substances are obtained when the toluenesulfonate of pseudo-tropine is used instead of the chlorotropane. This mixture of nitriles was converted by phenylmagnesium bromide to a pair of 2-allyl-1-methyl-5-phenylpyrrolidines. Quaternization, followed by a Hofmann degradation afforded a styrene which was reduced to the corresponding dihydro base, 4-dimethylamino-1-phenylheptane. The latter was synthesized by an independent route. This cleavage appears to be a variant of the 1–3 cleavages recently discussed by Grob[5] and therefore resembles the quinine–niquine transformation.[8]

In the course of some preparative work the need arose for a tropanyl nitrile. At that time an adequate supply of tropine was available and we transformed this alcohol to the corresponding chloride[2] in chloroform solution. The insoluble hydrochloride was converted to the free base before it was subjected to the action of aqueous alcoholic potassium cyanide. A sharply boiling liquid was obtained, whose analysis agreed with the formula $C_9H_{14}N_2$, but the infrared spectrum (Fig. 1) showed two cyanide bands in the 4.50 μ region and a band of moderate intensity at 6.08 μ. Further, the fingerprint region consisted of a series of blunted rather than crisp peaks which was also suggestive that a mixture rather than a pure compound was at hand. The nitrile group was converted readily to the corresponding methyl ester, but as in the case of the parent nitrile(s) it was difficult to obtain pure derivatives.

The action of phenylmagnesium bromide on the nitrile mixture resulted in the formation of another liquid, the analysis of which suggested the formula $C_{14}H_{19}N$. The over-all reaction appeared to be the replacement of the cyano group by a phenyl radical. This behavior is typical of α-dialkylaminoacetonitriles,[3] and it turned out that this structural

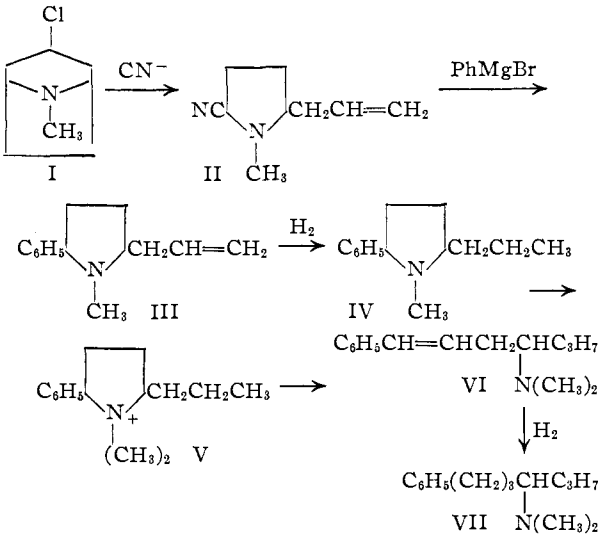
(1) A preliminary communication has been published; S. Archer, T. R. Lewis and Bernard Zenitz, THIS JOURNAL, **79**, 3603 (1957).

(2) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [4] **45**, 305 (1929).

(3) P. Bruylants, *Bull. soc. chim. Belg.*, **33**, 467 (1924); *C. A.*, **19**, 288 (1925).

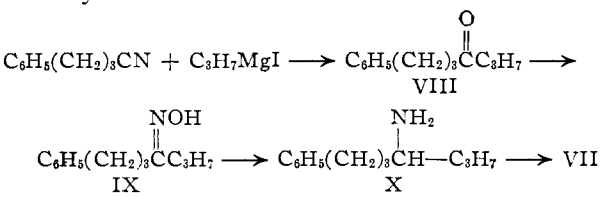
feature was present in the nitrile(s). The infrared spectrum was devoid of bands in the 4.50 μ area, but those associated with phenyl absorption and the 6.08 μ band were present (Fig. 1). This latter band was due to a monosubstituted terminal methylene group (confirmatory bands at 11.00 and 3.27 μ) and not a Schiff base since reduction which proceeded extremely rapidly furnished a dihydro compound which was not a secondary amine.

On the basis of the evidence just presented it is possible to assign structures to all the new reaction products. These are shown in the accompanying equations.



The base II has the correct empirical formula, a monosubstituted terminal olefin group, the dialkylaminoacetonitrile function and is capable of existing in two isomeric forms. Replacement of the cyano group by a phenyl radical gives base III, the structural features of which are compatible with its analysis and infrared spectrum. The dihydro compound then must be IV. The correctness of these assignments was supported by degradative work.[4]

The dihydro base IV was converted to a mixture of methiodides which was then degraded by the Hofmann method to a basic oil VI which absorbed at 253 mμ, the usual place for monosubstituted styrenes. The fact that a base was obtained from this reaction meant that the parent substance was cyclic. Catalytic hydrogenation resulted in the formation of a dihydro base VII which was devoid of absorbtive capacity at 253 mμ. This substance, characterized as the picrate, was synthesized by the method shown



(4) It may be mentioned that the sequence I through VI represents a new degradation of the tropane ring system, one that may be particularly useful in biogenetic work. Ozonolysis of VI should give benzaldehyde which contains as its carbonyl carbon C-1 of the tropane ring. Similar oxidation of II should give C-2 as formaldehyde.

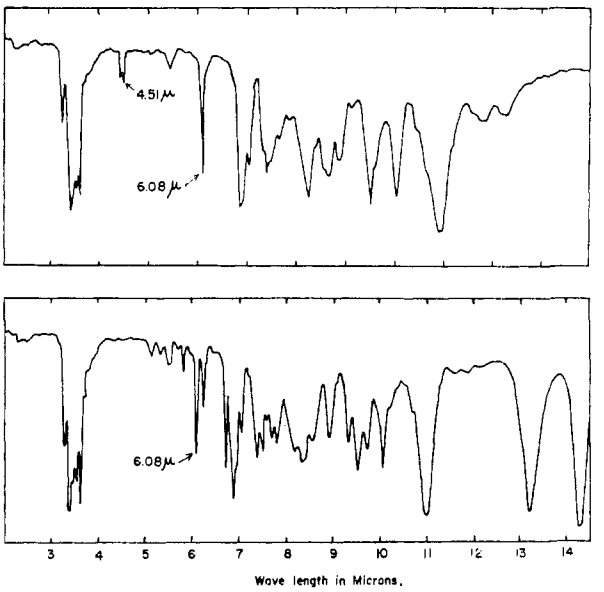
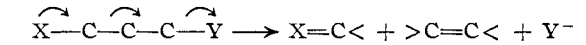


Fig. 1.—Top curve: infrared spectrum of 2-allyl-1-methylpyrrolidine nitrile mixture. Bottom curve: infrared spectrum of 2-allyl-1-methyl-5-phenylpyrrolidine mixture. Both samples run neat on a Perkin-Elmer model 21 instrument.

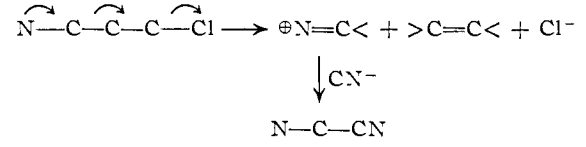
The reaction between *n*-propylmagnesium iodide and γ-phenylbutyronitrile furnished the heptanone VIII which yielded an oily oxime IX. The latter was reduced with lithium aluminum hydride to the primary amine X. This in turn was methylated by the Eschweiler-Clarke procedure to give the required base VII. The picrates obtained from both samples were identical in all respects.

The process whereby the tropanyl chloride I is transformed to the nitrile mixture II appears to be a new variant of a 1-3 cleavage illustrated by the general equation



This reaction has been the subject of at least two discussions[5,6] within the past year and several examples have come to light very recently.

In our case the specific atoms and the variation involved are shown in the equations



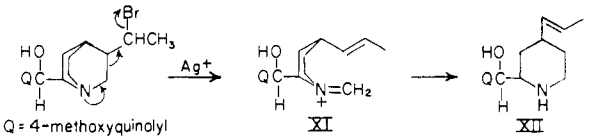
The closest analogous cases seem to be the cleavage of 1,1-diphenyl-2-methyl-3-piperidylpropyl chloride to 1,1-diphenylpropylene and the quinine-niquine transformation.[7,8]

(5) C. A. Grob, *Experientia*, **13**, 126 (1957).

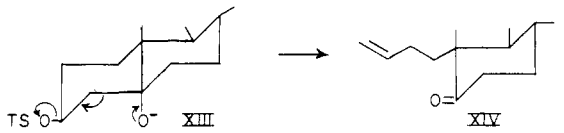
(6) L. H. Conover, "Symposium on Antibiotics and Mould Metabolites," Special Publication No. 5, The Chemical Society, London, 1956, p. 72.

(7) D. W. Adamson, *Nature*, **164**, 500 (1949).

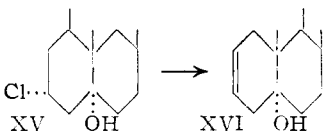
(8) R. B. Turner and R. B. Woodward, in Manske and Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1953, p. 21.



In this case silver ion assists in producing a cationoid center on the carbon bearing the halogen, the necessary electron shifts take place to produce the ion XI which loses formaldehyde to afford niquin, XII. It is difficult to evaluate the stereoelectronic factors from acyclic or semicyclic systems. Henbest[9] has studied the alkaline cleavage of cyclohexane-1,3-diol monosulfonates, wherein it has been possible to examine stereochemical effects. Thus the steroid tosylate XIII on treatment with potassium *t*-butoxide gave in addition to the 3,5-epoxide the *seco*-ketone XIV. The β-chloride corresponding to XIII gave the same mixture but at a slower rate. On the other hand, the epimeric chloride XV gave only the olefin XVI under similar

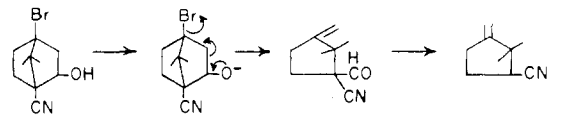


conditions. It was also shown that the stereochemistry at C-5 is of no consequence as a result of studies on simpler systems.[10]

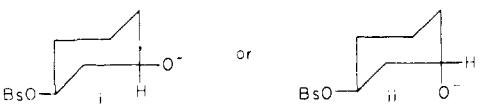


(9) R. B. Clayton, H. B. Henbest and M. Smith, *J. Chem. Soc.*, 1982 (1957).

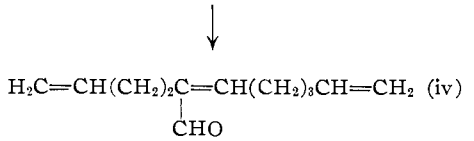
(10) In their work on the reaction



van Tamelen, *et al.*, THIS JOURNAL, **79**, 3839 (1957), surmised that the stereochemistry of the carbon–oxygen bond was not a critical factor. The necessary evidence has been supplied by Henbest (ref. 9). The *cis*- and *trans*-cyclohexanediol monobromobenzenesulfonates i and ii both yield the aldol iv, presumably *via* the intermediate iii. R. R. Burford, F. R. Hegwill and P. R. Jefferies, *J. Chem. Soc.*, 2937 (1957), carried out this cleavage in acid solution and were able to isolate a



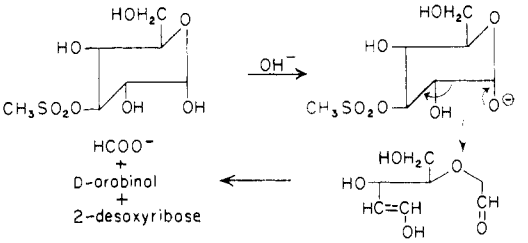
$[CH_2{=}CH(CH_2)_3CHO]$ (iii)



$H_2C{=}CH(CH_2)_2C{=}CH(CH_2)_3CH{=}CH_2$ (iv)
CHO

Thus in the steroid series ring A cleavage occurred when the C-3 tosylate bond and the C-4–C-5 bond were coplanar.

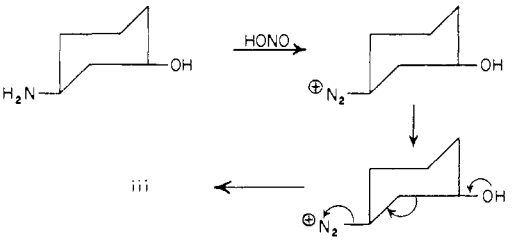
Smith[11] found that sodium hydroxide converted 3-O-methanesulfonylglucose to 2-desoxyribose, D-arabinal and formate ion. As Aspinall and Schwarz[12] pointed out, this reaction bears a strong resemblance to the steroid cleavage described above.



Accordingly, it is of some importance that the configuration of the tropanyl chloride be established. Pseudotropine and thionyl chloride give an isomeric tropanyl chloride[13] which reacts with potassium cyanide to furnish a pure crystalline nitrile which contains an intact tropane ring system. Pseudotropine and toluenesulfonyl chloride afforded a tosylate which reacted with cyanide ion to give a mixture of nitriles II. The infrared spectrum was virtually identical with that obtained previously. Since it is unlikely that inversion occurred in the preparation of the tosylate ester the reaction of tropine with thionyl chloride must have proceeded with inversion.[14]

Since the configurations of the two tropines are known[15] it follows that the C-3 halogen and the C-3 tosylate bonds are *trans* to and coplanar with the C-1–C-2 bond of the tropane ring, the one that is ruptured. Thus the significant stereochemical situation is the same as that in the steroid and other cyclic systems discussed above. The appended scheme is proposed to describe the course of the cleavage reaction.

The halide I or the corresponding tosylate undergoes the electron shifts indicated to produce a monomeric derivative of iii. Either *cis*- or *trans*-3-aminocyclohexanol on diazotization furnished this aldehyde, according to the scheme



On the other hand, Grob (ref. 5) seems to think that the configuration of the carbon-electron-donating center is of some importance. However, this conclusion was based on a study of an inadequate model.

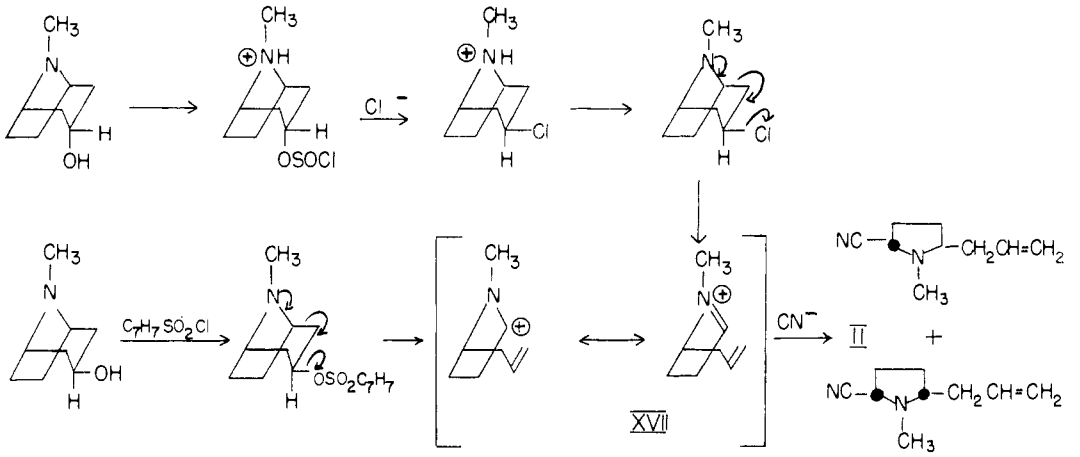
(11) D. C. C. Smith, *J. Chem. Soc.*, 2690 (1957).

(12) G. O. Aspinall and J. C. P. Schwarz, *Ann. Repts. of the Chem. Soc.*, **52**, 258 (1956).

(13) The reactions of this halide will be the subject of another communication.

(14) The reaction between thionyl chloride and alcohols in the presence of amines or amine hydrochlorides takes place by an SN2 type of displacement of the chlorosulfite ester by chloride ion; E. S. Lewis and G. M. Coppinger, THIS JOURNAL, **76**, 796 (1953); C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 392.

(15) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).



cationoid center at C-3. Rupture of the C-1–C-2 bond occurs in the by now accustomed way to give the resonating ion XVII which then adds cyanide ion in a non-stereospecific manner to furnish the observed mixture of pyrrolidine nitriles II.

Experimental[16]

3-Tropanyl Chloride.—A solution of 130.9 g. of thionyl chloride in 475 ml. of dry chloroform was added over a 30-minute period to a stirred solution of 70.6 g. of tropine in 475 ml. of chloroform kept at −10 to −20°. The bath was removed and the temperature of the solution was raised to 55–60°, whereupon the evolution of sulfur dioxide started and the desired salt began to separate. The mixture was kept at 60–70° for three hours, cooled and filtered. The salt was washed with acetone and dried; wt. 53.8 g., m.p. 239–240° dec.

The filtrates were united and taken to dryness. The residual dark oil was stirred with 100 ml. of dry acetone and the second crop of crystals was filtered, washed with acetone and dried; wt. 8.0 g., m.p. 237–238° dec.

The united crops (61.8 g.) were crystallized from 95% ethanol to give 55.2 g. of pure 3-chlorotropane hydrochloride, m.p. 242–243° dec.

Seventy-five grams of the above salt was converted to the free base by addition of potassium carbonate to an aqueous solution (125 ml.). The oil that separated was dissolved in pentane, filtered and distilled to furnish 56.0 g. of 3-chlorotropane, b.p. 60–61° (2.0 mm.), $n^{25}D$ 1.4998.

The picrate prepared in ethanol melted at 218–224° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{17}ClN_4O_7$: neut. equiv.,[17] 389. Found: neut. equiv., 389.

3-Pseudotropanyltoluenesulfonate Toluenesulfonic Acid Salt.—A solution of pseudotropine (14.1 g., 0.1 mole) in 25 ml. of dry alcohol-free chloroform and 8.0 g. of dry pyridine was cooled to −20° while 20 g. of *p*-toluenesulfonyl chloride in 25 ml. of the same grade chloroform was added with stirring over a period of one hour. The flask was then stoppered and kept at −5° for 3 days. The red magma that had formed was diluted with chloroform and then thoroughly shaken with ice-cold aqueous potassium carbonate solution. The layers were separated and the aqueous phase was washed with chloroform. The united oil layers were dried over potassium carbonate at 5°, filtered and then treated with a solution of 20 g. of toluenesulfonic acid monohydrate in 20 ml. of methanol. Ether was added to the yellow solution to turbidity. On chilling a crystalline solid separated which was collected and dried; wt. 34.5 g. (74%). After recrystallization from isopropyl alcohol there was obtained 23 g. of white crystals, m.p. 162–163.5°. This was pure enough for use in the next step. The analytical sample was obtained after one more recrystallization from isopropyl alcohol, m.p. 163–164°.

Anal. Calcd. for $C_{22}H_{29}NO_6S_2$: C, 56.51; H, 6.25; S, 13.71. Found: C, 56.50; H, 6.06; S, 13.70.

2-Allyl-5-cyano-1-methylpyrrolidine (II). A. From Tropanyl Chloride.—A solution of 22.1 g. of potassium cyanide in 85 ml. of water was heated under reflux for five hours with a solution of 51.0 g. of 3-chlorotropane in 225 ml. of ethanol. The suspension was cooled and filtered. The filtrate was concentrated to dryness leaving a mixture of an oil and inorganic salts. The oil was removed with pentane and then washed with water. The solution was distilled to give a total of 40.2 g. of the nitrile, b.p. 68–70° (2.0 mm.), $n^{25}D$ 1.4660–1.4668.

Anal. Calcd. for $C_9H_{14}N_2$: N, 18.65; N_{AP},[18] 9.33. Found: N, 18.35; N_{AP}, 9.38.

B. **From Pseudotropanyl Toluenesulfonate.**—A solution of 3.25 g. of potassium cyanide in 5.6 ml. of water was diluted with 20 ml. of ethanol and 4.5 g. of potassium bicarbonate and 21 g. (0.045 mole) of the toluenesulfonate ester were added in that order. The mixture was refluxed 16 hours and cooled. Solid potassium carbonate was added and the suspension was extracted with ether. The dried ether solution was distilled to give a fraction, b.p. 62–63° (1.0 mm.), which weighed 4.1 g. (61%), $n^{25}D$ 1.4656. The infrared spectra of the two samples are shown in Fig. 1a.

2-Allyl-3-carbomethoxy-1-methylpyrrolidine.—A rapid stream of dry hydrogen chloride was passed for 1 hour through a solution of 30 g. of the nitriles in 300 ml. of methanol containing 3.8 ml. of water. The solution was allowed to stand at room temperature for 24 hours. The ammonium chloride was removed and the methanol solution was concentrated to dryness. The residue was dissolved in 75 ml. of water and then saturated with potassium carbonate. The oil was removed with chloroform and distilled to give 21.7 g. of the methyl ester, b.p. 67–70° (2.0 mm.), $n^{25}D$ 1.4610.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.38; H, 8.97; N, 7.59.

2-Allyl-1-methyl-5-phenylpyrrolidine (III).—A Grignard reagent prepared from 26.7 g. of bromobenzene and 4.6 g. of magnesium in 150 ml. of ether was treated with 100 ml. of an ethereal solution of 18 g. of 2-allyl-5-cyano-1-methylpyrrolidine.[3] The mixture was heated for one hour before the ether was replaced with benzene. The suspension was refluxed for 3 hours and then allowed to cool overnight. The mixture was decomposed with the aid of 120 ml. of 6 *N* hydrochloric acid. The whole was heated on the steam-bath for two hours, cooled and allowed to separate. Three layers appeared, but after the removal of the acid layer the addition of water to the top layers caused the disappearance of the middle phase. After further extraction with dilute hydrochloric acid the benzene solution was discarded. The aqueous portions were made basic with ammonia and the base that separated was removed with ether. After drying, the solution was distilled to yield a fraction, b.p. 81–90° (0.5 mm.), wt. 17.8 g. Upon redistillation the oil boiled at 69–70° (0.1 mm.), $n^{25}D$ 1.5235.

(16) Analyses were carried out under the supervision of Mr. K. D. Fleischer of this Institute. We wish to thank Miss C. M. Martini, Mr. M. Priznar and Dr. F. C. Nachod for the required spectral work; and Professor William S. Johnson for very profitable discussions.

(17) Neutral equivalents were determined by titration of the picric acid with sodium methoxide.

(18) Acetic–perchloric acid titration of basic nitrogen.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.70; H, 9.81; N, 6.84.

1-Methyl-2-phenyl-5-propylpyrrolidine (IV).—A solution of 10.4 g. of the above pyrrolidine in 200 ml. of absolute ethanol was hydrogenated in the presence of 200 mg. of Adams platinum oxide catalyst. One mole of hydrogen was consumed in 5 minutes. The mixture was worked up as usual to furnish 8.5 g. of the dihydro base, b.p. 111–113° (4 mm.), $n^{25}D$ 1.5090.

Anal. Calcd. for $C_{14}H_{21}N$: N, 6.86. Found: N, 6.90.

4-Dimethylamino-1-phenyl-1-heptene (VI).—The above dihydro base IV (13.3 g.) was covered with 50 ml. of methyl iodide. The solution warmed spontaneously and then deposited a yellow gum. The methyl iodide was allowed to evaporate and the residue was treated with enough fresh methyl iodide to just cover it. The mixture was warmed and after all the methyl iodide had evaporated the gum was dissolved in warm acetone. On cooling a white solid, m.p. 126–130°, deposited; wt. 14.7 g.[19]

Silver oxide was freshly prepared from 12.6 g. of silver nitrate and washed thoroughly with distilled water. The mixture of methiodides (m.p. 126–130°, wt. 12.0 g.) was dissolved in 100 ml. of water and heated on the steam-bath with the silver oxide for one hour. The solids were collected on a filter and digested for 15 minutes with 50 ml. of hot water. The united aqueous extracts were evaporated at 45° (1 mm.). The residue was dissolved in methanol, freed of a small amount of insoluble material and distilled at a pressure of 0.3 mm. A liquid distilled at 83–100°; wt. 5.0 g.

On redistillation there was obtained a fraction, b.p. 125–128° (4.0 mm.), $n^{25}D$ 1.5200. The ultraviolet absorption spectrum showed ϵ_{253} 11,650.

Anal. Calcd. for $C_{15}H_{23}N$: N, 6.46. Found: N, 6.44.

4-Dimethylamino-1-phenylheptane (VII).—The above styrene (2.3 g.) was reduced in 200 ml. of 95% ethanol in the presence of 100 mg. of Adams platinum oxide. When the reduction was over, an aliquot was removed for ultraviolet spectral analysis (ϵ_{253} 219).

The remainder of the solution was concentrated to dryness and the residue was treated with alcoholic picric acid. After three recrystallizations from ethanol the salt melted at 92.5–94° and did not depress the m.p. of the authentic specimen described below.

Anal. Calcd. for $C_{21}H_{28}N_4O_7$: N, 12.49. Found: N, 12.23.

1-Phenyl-4-heptanone (VIII).—N-Propylmagnesium iodide was prepared in 400 ml. of ether from 68 g. of propyl iodide and 10.2 g. of magnesium turnings. A solution of 43.5 g. of γ-phenylbutyronitrile in 100 ml. of ether was added dropwise. The ether was replaced by dry benzene and the mixture was refluxed for three hours. The mixture was treated with 200 ml. of 6 *N* hydrochloric acid and refluxed for 5 hours. The layers were separated and the benzene solution was washed with water, dried and distilled to give 23 g. of the desired ketone, b.p. 95–108° (0.3–0.5 mm.). Redistillation gave a pure product, b.p. 96–98° (0.1 mm.), $n^{25}D$ 1.5022.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.07; H, 9.43.

The 2,4-dinitrophenylhydrazone melted at 85–87° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: NO_2, 24.8. Found: NO_2, 24.3.

4-Dimethylamino-1-phenylheptane (VII).—Twenty-two grams of the heptanone was treated with 10 g. of hydroxylamine hydrochloride in 100 ml. of pyridine. The solution was heated on the steam-bath for 3 hours. The pyridine was removed *in vacuo* and the residue was partitioned between benzene and water. The benzene phase was washed with water and concentrated to leave 23 g. of a red oil which was used directly in the next step.

Twenty grams of lithium aluminum hydride was covered with 750 ml. of dry ether and treated with an ethereal solution of the crude oxime. The mixture was refluxed 6 hours and allowed to stand overnight. The mixture was treated dropwise with 20% rochelle salt solution and after the vigorous reaction had subsided the whole was stirred for several hours. It was filtered and the cake was washed with ether. The ether solution was separated and concentrated to 200 ml. before being extracted repeatedly with dilute hydrochloric acid. The united acid extracts were made alkaline and the oil removed with ether. The dried solution was distilled to give 7.6 g. of the amine, b.p. 93–95° (0.1 mm.). This was used directly in the next step without further purification. Seven grams of the 1-phenyl-4-aminoheptane was dissolved in 14.5 ml. of 98% formic acid and treated with 17 ml. of 37% formalin. After the initial vigorous reaction had subsided the solution was heated on the steam-bath for 5 hours. The solution was concentrated *in vacuo* to leave an oily residue which was dissolved in water and basified with sodium hydroxide solution. The oil was extracted with ether, dried over sodium sulfate and distilled to give 5.0 g. of a colorless liquid, b.p. 100–110° (0.1 mm.). The picrate which was prepared in ethanol melted at 92.5–93° after two recrystallizations from ethanol. A mixture with the picrate described previously melted at 92.5–94°.

RENSSELAER, NEW YORK

(19) By a suitable modification of this technique it was possible to obtain two methiodides. A solution of 6.2 g. of the dihydro base III in excess methyl iodide was allowed to stand at room temperature for about one hour and then was filtered. The insoluble gummy material was washed with cold acetone, whereupon it was transformed to a white crystalline material, m.p. 135–140°, wt. 6.5 g. The filtrate was diluted with more methyl iodide and allowed to stand overnight. Yellow plates had separated; wt. 4.5 g. These crystals dissolved in acetone readily and on standing the solution deposited a white crystalline material, m.p. 172–174°. After recrystallization from acetone the compound melted at 173–174°. *Anal.* Calcd. for $C_{15}H_{29}IN$: I, 36.1. Found: I, 36.0.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reactions of Orthoesters with Aryl Isocyanates

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Phenyl isocyanates were found to react with triethyl orthoformate to yield 1,3-diaryl-5,5-diethoxyhydantoins. 1-Naphthyl isocyanate and triethyl orthoformate gave 1-(α,α,α-triethoxy)-acetyl-1,3-di-1′-naphthylurea. Phenyl isothiocyanate and triethyl orthoacetate yielded 1,3-diphenyl-6-ethoxy-2,4-dithiouracil. This uracil also was prepared from phenyl isothiocyanate and ketene diethylacetal. Phenyl isocyanates reacted spontaneously with ketene diethylacetal to form β,β-diethoxyacrylanilides.

The previously described reactions of orthoesters, including those with Grignard reagents, all occur by replacement of one or more of the alkoxy groups of the orthoester.[1] This indicates that the α-hydrogen of triethyl orthoformate and also the β-hydrogens of triethyl orthoacetate are not easily replaced. This paper is a description of the reactions of aryl isocyanates with triethyl orthoformate and triethyl orthoacetate involving replacement of the α- and β-hydrogens of these orthoesters.

When triethyl orthoformate was allowed to re-

(1) A. E. Tschitschibabin and S. A. Jelgasin, *Ber.*, **47**, 48 (1914).