$$Br\cdot + RH \longrightarrow BrH + R\cdot$$
$$BrH + Ar_2C{=}NBr \longrightarrow Ar_2C{=}NH + Br_2$$
$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot$$

The competing reactions

$$Br_2 + 2Ar_2C{=}NH \rightleftharpoons Ar_2C{=}NBr + Ar_2{=}NH_2{}^+Br^-$$

provide an additional complication. Benzyl bromide was shown to react with benzophenone imine in boiling toluene to give after 5 hr 17% of benzophenone N-benzylimine V and 18% of benzophenone imine hydrobromide, a reaction which may explain the small amounts of V found in the bromination reactions.

Experimental Section[6]

Benzophenone N-bromimine (I), mp 37–38° (petroleum ether bp 30–60°; lit.[7] mp 38.5°), was prepared from benzophenone imine and bromine in aqueous sodium carbonate solution.

Benzophenone N-chlorimine (II), mp 35–36° (petroleum ether bp 30–60°; lit.[8] mp 37°), was obtained by chlorination of benzophenone imine with chlorine in aqueous sodium bicarbonate.

Reactions of Bromimine I with Cyclohexane, Cyclohexene, and Toluene.—Cyclohexane and cyclohexene were heated with calcium hydride under reflux for several hours, fractionally distilled, and then stored over calcium hydride. Toluene (reagent grade) was treated for several hours with calcium hydride but not distilled. The bromimine I was recrystallized shortly before being used. Its purity was checked by a melting point determination and iodometric titration. Glassware was washed in chromic acid cleaning solution, rinsed with dilute, aqueous ammonia and distilled water, and dried in an oven at 130°. Reactions were carried out in a nitrogen atmosphere.

Characterization of the products was achieved by filtration of the imine hydrobromide salt IV·HBr (identified by comparison with an authentic sample) and separation of the other components by gas phase chromatography in sufficient quantity to permit determination of their infrared, nmr, and ultraviolet spectra. The quantitative determination of benzyl bromide was made by nmr with phthalide as an internal standard and working from an experimentally determined plot of ratio of areas of the CH_2 absorptions against composition. Average values of six to ten integrations were used. Benzophenone imine was determined by precipitation as the hydrochloride with dry hydrogen chloride and corrected for hydrochloride formed by the reaction of hydrogen chloride with unreacted N-bromimine. The unreacted N-bromimine was determined by iodometric titration. Benzophenone benzylimine was determined by an nmr method analogous to that used with benzyl bromide. Benzophenone azine was determined by ultraviolet spectroscopy by diluting an aliquot of the reaction mixture with ethanol and determination of the absorption at 350 mμ where none of the other known products absorbed.

Reagent grade bromobenzene was used as an internal standard in the gas phase chromatographic analyses of 3-bromocyclohexene and bromocyclohexane which were carried out on a 4-ft SE-30 silicone column under conditions such that the internal standard and sample had similar retention times but were completely resolved. Standard curves were employed and ratios of average areas from three injections were used. Results are presented in Table I.

Irradiation of 122 mg of bromimine I in 3.0 ml of dry benzene under reflux with a G.E. sunlamp gave a deep yellow color after 2 min and after 4.0 hr the ultraviolet spectrum of an aliquot diluted with ethanol showed an absorbance at 350 mμ corresponding to 26 mg (30%) of azine VI.

Reactions of Benzophenone N-Chlorimine (II).—Reactions were carried out with equipment open to the atmosphere and exposed to ordinary laboratory lighting. Starch–iodide tests showed that none of the reactions were complete after 50 hr. Analyses were carried out by concentration of the solution and analysis by gas phase chromatography with a 10-ft Dow-11 silicone column. Standard solutions of cyclohexyl chloride in cyclohexane and benzyl chloride in toluene were prepared and injected alternately with the sample. The results, based on averages of three to five sets of areas, are presented in Table I.

Reaction of Benzophenone N-Bromimine (I) **with Hydrogen Bromide. Benzophenone Imine Hydrobromide** (IV·HBr).—A solution shown by titration with 0.10 *N* sodium hydroxide to contain 0.75 mmole of hydrogen bromide in dry benzene was added dropwise with stirring to 215 mg (0.83 mmole) of bromimine in dry benzene. The color of bromine was apparent with the addition of the first drop and a fine, white precipitate was visible after the addition of 2 or 3 drops. After the addition was complete the precipitate was collected, washed with benzene, and dried at 130°. The imine hydrobromide (IV·HBr) so collected amounted to 0.36 mmole or 48% based on the hydrogen bromide employed. The reaction was also observed to be instantaneous at −78°.

Anal. Calcd for $C_{13}H_{12}BrN$: C, 59.6; H, 4.6; N, 5.4. Found: C, 59.9; H, 4.6; N, 5.3.

Reaction of Benzophenone Imine (IV) **with Benzyl Bromide.**—A solution of 179 mg of benzophenone imine and 184 mg of benzyl bromide in 3.0 ml of toluene was heated under reflux for 5 hr under nitrogen in the dark with stirring. Determination of the amount of the hydrobromide salt IV·HBr and N-benzylimine V by the methods described previously for the bromination reactions gave values of 18 and 17% based on the imine IV.

Reaction of Bromimine I with Benzaldehyde.—A solution of 160 mg of freshly distilled benzaldehyde and 262 mg of bromimine I in 3.0 ml of benzene was stirred, heated under reflux in a nitrogen atmosphere, and illuminated with a G.E. sunlamp 6 in. from the flask. Within 1 min the solution had turned deep orange, a precipitate had appeared within 2 min, and the starting material had been totally consumed (starch–iodide) after 10 min. Filtration gave 116 mg (44%) of hydrobromide IV·HBr. Removal of a portion of the solvent gave a residue of which the infrared spectrum agreed with that of benzophenone N-benzoylimine,[9] but with a few extra bands of minor intensity. Analysis by gas phase chromatography with a 4-ft SE-30 silicone column (with a standard solution) indicated the presence of 143 mg (50%) of N-benzoylimine (VII).

(6) Melting points are corrected. Infrared spectra were obtained in part by Mr. Dick Johnson and his associates with a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were obtained with a Bausch and Lomb Spectronic 505 or, in part, by Mr. P. Hon with a Cary Model 14M spectrophotometer. Vapor phase chromatography was carried out with an Aerograph A-300 dual-column instrument equipped with a Brown recorder and Disc integrator. Important spectra and other detailed data may be found in the Ph.D. thesis of C. G. McCarty[1] available on microfilm from University Microfilms, Ann Arbor, Mich.

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A Convenient Preparation of Pyrrolizidine by Reductive Cyclization

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Pyrrolizidine compounds are of interest chiefly because of the occurrence of this bicyclic ring system in a number of alkaloids.[2] Although many syntheses of the simpler derivatives are known,[3,4] with one recent exception[5] they are uniformly inefficient in terms of the

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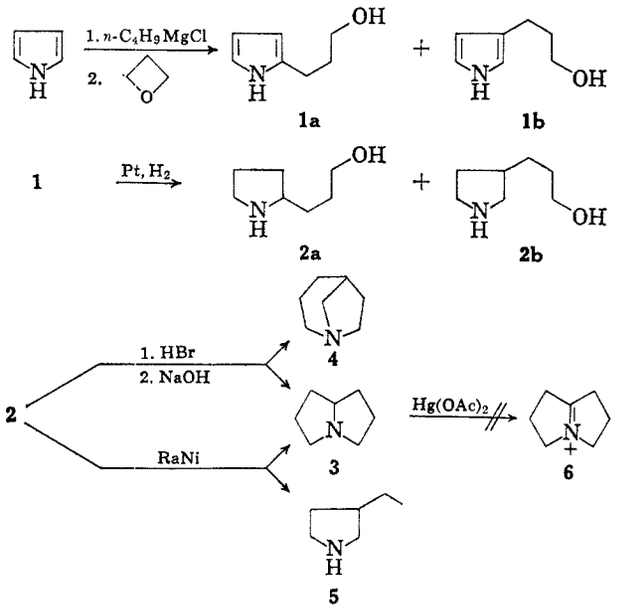

over-all yield and especially the number of steps from readily available starting materials. This paper reports a short, convenient preparation of pyrrolizidine (**3**) by means of the reductive cyclization procedure previously utilized for the synthesis of a variety of indolizidines and quinolizidines.[6]

Because of the number of steps[7] or low conversions[8] in previous syntheses of the required starting material, 2-(3-hydroxypropyl)pyrrolidine (**2a**), a new method of preparation was undertaken. Reaction of pyrrylmagnesium chloride with trimethylene oxide produced, in 40% yield,[9] a 4:1 mixture of two components, presumably the 2- and 3-(3-hydroxypropyl)pyrroles **1a** and **1b**, respectively. The major constituent of this mixture was shown to be the 2 isomer by catalytic reduction to a 4:1 mixture of the pyrrolidylpropanols **2a** and **2b** (96% yield) which was cyclized *via* the bromide–hydrobromide to pyrrolizidine (**3**) and 1-azabicyclo[3.2.1]octane (**4**) in yields of 45 and 19%, respectively. This predominance of the 2 isomer is consistent with previous results on alkylation of the pyrrole Grignard reagent.[10]

The Raney nickel cyclization of the pyrrolidylpropanol mixture **2** to pyrrolizidine (**3**) proceeded in 49% yield. Although this is only slightly better than the yield obtained by the bromide–hydrobromide procedure (45%) described above, the work-up is greatly facilitated since no other tertiary amines are formed thus permitting separation by the Schotten–Baumann procedure. The other basic products of the reductive cyclization of the mixture **2** appear to be secondary amines (infrared) one of which was identified as 3-ethylpyrrolidine (**5**). This latter compound presumably arises by dehydroxymethylation of **2b**, a common process when the proposed intermediates in the reductive cyclization would have prohibitive strain.[6] Similar steric effects also may be responsible for the lower yield of pyrrolizidine than of indolizidine and quinolizidine by the reductive cyclization procedure.[6] In support of this hypothesis, it was not possible to oxidize pyrrolizidine (**3**) to the corresponding iminium salt (**6**) with mercuric acetate even under conditions more severe than those utilized for the oxidation of indolizidine and quinolizidine.[6]

(6) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964).

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(9) The much lower yields of product from the reaction of pyrrylmagnesium chloride with ethylene oxide obtained by K. Hess, F. Merch, and Cl. Ulbirg [*Chem. Ber.*, **48**, 1886 (1915)] may be due to the solubility of the material in aqueous solutions and/or difficulty in extracting from suspensions of $Mg(OH)_2$. These problems were circumvented in the present work by the use of continuous liquid–liquid extraction (see the Experimental Section).

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Experimental Section[11]

Pyrrylpropanols 1a and 1b.—To an ether solution of *n*-butylmagnesium chloride (0.86 mole) prepared by conventional[12] methods from 80 g of *n*-butyl chloride and 21 g of magnesium turnings in a 1-l., three-necked Morton flask equipped with a reflux condenser, dropping funnel, and mechanical stirrer, was added 58 g (0.86 mole) of freshly distilled pyrrole. After the evolution of gas had ceased, the flask was cooled in an ice bath and 25 g (0.43 mole) of trimethylene oxide in 75 ml of ether was slowly added with stirring. The reaction mixture was stirred at room temperature for 45 min, heated at reflux for 3 hr, and cooled, 200 ml of water was added, and the resulting mass was continuously extracted with ether[13] for 3 days. The dried ether extracts were distilled through a Vigreux column to give some unreacted pyrrole and 21.5 g (40%) of a colorless, viscous oil, bp 125–128° (1 mm), which darkened rapidly on exposure to air. Vapor phase chromatography indicated the presence of two products in *ca.* 4:1 ratio the compound of higher retention time (**1a**) predominating.

Anal. Calcd for $C_7H_{11}NO$ (**1a** + **1b**): C, 67.17; H, 8.86. Found: C, 66.91; H, 8.54.

Pyrrolidylpropanols 2a and 2b.—A solution of 10 g of the freshly distilled mixture of **1a** and **1b** (the darkened product was not completely reduced) in 100 ml of glacial acetic acid containing 1 g of platinum oxide was hydrogenated in a medium pressure Paar apparatus at *ca.* 60 psi of initial pressure. After the theoretical pressure drop had been realized (4–5 hr), the catalyst was removed by filtration and the solvent was removed by evaporation on a rotary evaporator. The residue was heated under reflux for 2 hr with 100 ml of 30% sodium hydroxide solution to saponify any acetate ester which might have formed.[6] The reaction mixture was extracted with three 75-ml portions of chloroform which were combined, dried with anhydrous potassium carbonate, and then distilled through a Vigreux column to give 9.9 g (96%) of a colorless oil, bp 80–83° (1.0 mm). Vapor phase chromatography indicated a *ca.* 4:1 mixture with the product of lower retention time (**2a**) predominating.

Anal. Calcd for $C_7H_{15}NO$ (**2a** + **2b**): C, 65.06; H, 11.71. Found: C, 65.16; H, 11.86.

Cyclization of Pyrrolidylpropanol Mixture 2a and 2b. A. Raney Nickel Method.—A sample (10.5 g) of the above mixture of **2a** and **2b** was subjected to the general cyclization procedure[6] except that the reaction was stopped after 1500 ml of distillate had been collected even though fresh distillate was still slightly basic to litmus. Work-up of the distillate in the usual manner[6] gave 4.4 g of a colorless oil which displayed four peaks on vapor phase chromatography whose areas were in the ratio 3:1:1:12 in order of increasing retention time. The products of highest and lowest retention time were separated by preparative vpc and identified as pyrrolzidine [**3**, picrate mp 253–255° dec (lit.[14] mp 253–257°), chloroplatinate mp 204–205° (lit.[14] mp 204–205°)] and 3-ethylpyrrolidine [**5**, picrate mp 102–103° (lit.[15] mp 102–103°), chloroplatinate mp 162–163° (lit.[15] mp 162–163°)], respectively. The infrared spectra of the two minor products had peaks in the N–H region (3200 cm^{-1}).

For preparative purposes the above oil was mixed with 4 g of benzenesulfonyl chloride and steam distilled from 100 ml of a

(11) Melting points are corrected; analyses were performed by Mr. C. F. Geiger, Ontario, Calif. Vapor phase chromatography was carried out on a Wilkens Aerograph A-90-C with a 10-ft, 10% silicone on Fluoropack column.

(12) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," 2nd ed, Prentice-Hall Co., Inc., New York, N. Y., 1962, p 462.

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10% sodium hydroxide solution until the distillate was no longer basic to litmus (200 ml). The distillate was saturated with potassium carbonate and extracted with three 100-ml portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and the ether was removed by distillation to leave 3.6 g (49% based on the amount of **2a** present in the starting pyrrolidylpropanol mixture) of vpc pure pyrrolizidine (**3**).

B. Bromide–Hydrobromide Method.[16]—The solution obtained by adding, with cooling and stirring, 50 ml of cold 48% hydrobromic acid to 7.9 g of the pyrrolidylpropanol mixture **2a** and **2b** was distilled through a Vigreux column until the boiling point reached 99°. The distilland was evaporated to dryness with a rotary evaporator and the resulting dark brown residue was taken up in 50 ml of water which was then added to a solution of 20 g of sodium hydroxide in 150 ml of water. This reaction mixture was steam distilled until the distillate was no longer basic to pH paper. Extraction of the potassium carbonate saturated distillate with three 100-ml portions of ether, followed by drying (potassium carbonate) and distillation of the combined ether extracts through a Vigreux column, afforded 4.7 g of a colorless oil whose vapor phase chromatogram indicated a 7:3 mixture of two components in order of increasing retention time. These components were separated by preparative vpc and identified as pyrrolizidine (**3**) and 1-azabicyclo[3.2.1]octane [**4**, picrate mp 293–295° dec (lit.[17] mp 294–295°), chloroplatinate mp 214–215° (lit.[17] mp 215–215.5°)], respectively.

Attempted Mercuric Acetate Oxidation of Pyrrolizidine (3).—In a 100-ml, three-necked flask fitted with a mechanical stirrer, reflux condenser, and addition funnel was placed 50 g (0.155 mole) of mercuric acetate and 50 ml of 5% aqueous acetic acid. The apparatus was evacuated and refilled with nitrogen several times and warmed until all of the mercuric acetate had dissolved. To the resulting solution was added 2.5 g (0.022 mole) of pyrrolizidine (**3**) and the mixture was heated to reflux with stirring for 48 hr. Upon cooling only a very small amount of mercurous acetate precipitated. The reaction was worked up in the usual manner[6] to afford 1.75 g (70%) of a yellow oil whose infrared spectrum showed no C=C or vinyl hydrogen absorption and which was identical with that of pyrrolizidine (**3**). Vapor phase chromatography similarly indicated no product other than pyrrolizidine.

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The Formation of 2-Aroylpyrroles from Sodiopyrrole and Aromatic Aldehydes

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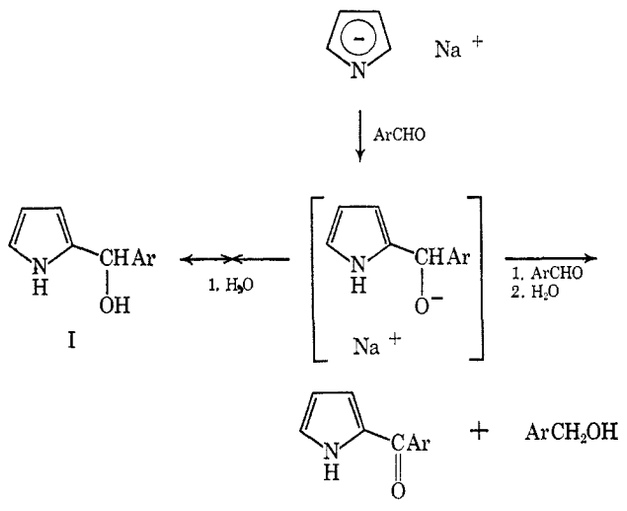
It has been found that the sodium derivative of pyrrole does not give the expected alcohols (I) when allowed to react with aromatic aldehydes, but yields ketones (II). A second product of this reaction is the alcohol (III) corresponding to the reduction product of the aromatic aldehyde employed.

The probable reaction route is related to an alkoxide reduction which frequently takes place during the reaction of Grignard reagents and aldehydes.[1] This type of reaction is a special case of the Meerwein–Ponndorf–Verley reduction[2] or an Oppenauer oxidation[3] in which the intermediate, sodium salt of α-pyrrol-2-ylbenzyl alcohol, is converted into II while a second mole of aromatic aldehyde is reduced to compound III.



IV, Ar = C_6H_5
V, Ar = p-$CH_3OC_6H_4$
VI, Ar = m-ClC_6H_4

The reaction was carried out employing equimolar quantities of the sodium derivative of pyrrole and the aromatic aldehyde which was added to it. No significant change in yield took place when 2 moles of the aromatic aldehyde were added to 1 mole of the sodium derivative of pyrrole.

The ketones IV and V are reported structures having melting points and infrared spectra in agreement with the literature.[4,5] The alcohols were characterized by comparison of their infrared spectra with those of authentic samples (see Table I).

TABLE I
INFRARED SPECTRAL DATA OF AROYLPYRROLES

	$CHCl_3$[a]		$CHCl_3$		KBr	
Compd	νNH, cm⁻¹	νC=O, cm⁻¹	νNH, cm⁻¹	νC=O, cm⁻¹	νNH, cm⁻¹	νC=O, cm⁻¹
IV	3445	1615	3460	1620	3290	1626
V	3450	1620	3460	1605	3300	1610
VI			3460	1622	3300	1621

[a] Literature values from ref 4.

Experimental Section

The General Procedure for the Preparation of 2-Aroylpyrroles.—Pyrrole (0.5 mole, 33.5 g) was added slowly to a stirred refluxing suspension of sodium amide (0.5 mole, 19.5 g) in benzene (500 ml) under a nitrogen atmosphere. Upon completion of the addition of pyrrole, followed by refluxing for 16 hr, the aromatic aldehyde (0.5 mole) was introduced in a dropwise manner to the cooled, stirred suspension. After the aromatic aldehyde addition was completed, the reaction was refluxed for 1 hr and cooled, and water (200 ml) was added cautiously. The layers were separated and the organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed in a rotary evaporator.

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