Calculations.—If a is the molecular ratio of α-phenylbutyric anhydride to the alcohol (the usual ratio was 2.5–3), fully stereoselective esterification will give an acid whose $[\alpha]_D = 96.5°/2a - 1$ since the specific rotation (benzene) of optically pure α-phenylbutyric acid is ±96.5°.[7] The optical yield is the ratio of the experimentally observed specific rotation to this theoretical value.

Example. Absolute Configuration of 1-Epiallohelenalin (2).—A solution of 207 mg of α-phenylbutyric anhydride (5.83×10^{-4} mole) and 59.4 mg of 2 (2.23×10^{-4} mole), in 2.5 ml of pyridine was allowed to stand overnight at room temperature. Excess anhydride was destroyed by adding 1 ml of water and allowing to stand for 6 hr at room temperature. The solution was extracted with ether (use of ethyl acetate is also feasible). The extract was washed with water, three 10-ml portions of 5% sodium bicarbonate solution, and again several times with water. The combined aqueous extracts were washed with chloroform and acidified with an excess of 1 *N* sulfuric acid solution. The acidified solution was extracted with chloroform and the chloroform extract was dried and evaporated. This afforded 90.0 mg (constant weight after drying *in vacuo*) of α-phenylbutyric acid (pure on tlc), α_D in 5 ml of benzene (1-dm tube) +0.061 ± 0.002°, $[\alpha]_D$ +3.4°, theoretical $[\alpha]_D = 95.6°/[2(2.61) - 1] = +22.8°$. The optical yield therefore was 3.4/22.8 = 14.9% (+).

The neutral fraction in ether was washed thoroughly with water, 1 *N* sulfuric acid, and again with water and evaporated. The residual ester (77.1 mg) contained no starting material, as demonstrated by nmr spectroscopy.

Acknowledgment.—H. B. K. thanks Professor T. J. Mabry for the opportunity to carry out part of this work in the Department of Botany, University of Texas, Austin, Texas, and acknowledges a NATO grant during 1965. We thank Professor A. Horeau for useful discussion and for private communication of unpublished results.

A Novel Condensation Reaction of α,β-Unsaturated Cyclic Ketones with Ammonium Thiocyanate

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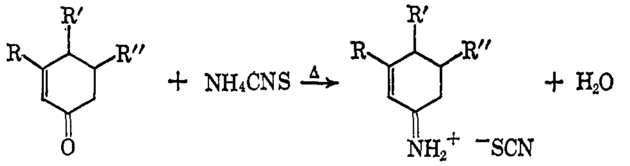
The reaction of ammonium thiocyanate with α,β-unsaturated aliphatic ketones (*e.g.*, mesityl oxide and styryl alkyl ketones) is little known in the literature.[2-4] The reaction products are substituted 2-mercaptodihydropyrimidines. In the present study, the condensation of 3-substituted 2-cyclohexen-1-ones with ammonium thiocyanate has been examined and the structure of the products has been established.

The condensations are conducted by heating 1 mole equiv of both the alicyclic unsaturated ketone and ammonium thiocyanate in a nonpolar solvent with azeotropic removal of the water formed. It was found that by carrying out the reaction in refluxing toluene, suitable reaction conditions are met. The products of the reaction are imine hydrothiocyanates.



The reaction is heterogeneous (ammonium thiocyanate and the imine hydrothiocyanates are insoluble in the hydrocarbon medium) and the addition of polar solvents reduces the yields considerably.

The formation of these alicyclic α,β-unsaturated imine hydrothiocyanates seems particularly influenced by the nature of the alicyclic ketone. Thus, whereas the ketones reported in Table I give the imines in very good yields, 2-cyclohexen-1-one and carvone only yield oily products, from which the corresponding pure imine hydrothiocyanate could not be isolated, and 2-phenyl-2-cyclohexen-1-one does not react at all with ammonium thiocyanate. Most probably, the α,β-unsaturated alicyclic imine hydrothiocyanates need a substituent on the 3 position for their stabilization. A bulky group on the 2 position hinders the reaction completely.

During the investigation of the condensation of isophorone with ammonium thiocyanate it was found that the reaction is favored by the addition of 1–3% by weight of sodium salts of phosphoric acid; *i.e.*, the yield of the condensation product increased from 60 to 85%. Sodium chloride and sodium sulfate show the same effect. Presumably, these inorganic salts stabilize the imine hydrothiocyanate as ammonium thiocyanate is stabilized by sodium phosphate.[5] Table I summarizes examples of the present study.

TABLE I

CONDENSATION OF α,β-UNSATURATED KETONES WITH AMMONIUM THIOCYANATE

	Imine hydrothiocyanates			
Ketone	Mp, °C	Yield, %	Pic,[a] mp, °C	Infrared, cm^{-1} [b]
Isophorone	96–97	85	165–166	2040
3-Methyl-2-cyclohexen-1-one	87–88	86.5	168–169	2070
3,5-Dimethyl-2-cyclohexen-1-one	115–116	84.5	155–156	2065
3-Phenyl-2-cyclohexen-1-one	134–135	81.5	195–196	2075
10-Methyl-1(9)-octalone-2	115–116	82.0	154–155	2070

[a] Pic = picrate of the imine. [b] Infrared absorption band of the imine hydrothiocyanate group observed as a KBr disk.

These five imine hydrothiocyanates prepared here have an orange-yellow color and are characterized by three specific bands in the infrared spectrum (observed in a KBr disk) at 2050 ± 20, 1650 ± 10 (assigned to olefinic double bond), and 1610 ± 20 cm^{-1} (assigned to C=N stretching). The band at 2050 ± 20 cm^{-1} is a characteristic bond for ionic thiocyanates such as ammonium or sodium thiocyanates (2050 cm^{-1}), whereas organic thiocyanates (covalent) usually show bands at 2240 cm^{-1}. In agreement with their ionic property, they are all very soluble in polar solvents. Their aqueous or ethanolic solutions are stable at room temperature for several days but the addition of a base, such as sodium bicarbonate, to their aqueous solutions causes hydrolysis at room temperature yielding the corresponding α,β-unsaturated ketone. On the other hand, their stability toward acids is greater; thus an acidified solution (acetic acid) must be heated before

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[1] J. R. Geigy A. G., Basle, Switzerland.

[2] T. E. Robbins, U. S. Patent 2,539,480 (1951).

[3] W. H. Hill, British Patent 633,353 (1949).

[4] K. C. Robert and R. J. Moualim, British Patent 654,609 (1951).

[5] W. H. Hill and J. H. F. Veltman, U. S. Patent 2,440,717 (1948).

hydrolysis can be observed. The free imines could not be isolated as such but their picrates could be formed and characterized.

3,5,5-Trimethyl-2-cyclohexen-1-imine hydrothiocyanate, derived from isophorone, wasc hosen for detailed structure elucidation studies. The nmr spectrum taken in deuterated chloroform exhibits six peaks showing no significant fine structure. The experimental ratios are 6.1:3.2:2.0:2.0:0.94:2.0 at τ 8.90, 7.86, 7.64, 7.28, 3.40, and −0.54, respectively. These peaks are assigned to *gem*-dimethyl, allylic methyl, two discrete allylic methylenes, olefinic, and imine protons. These peaks are shifted to lower fields than similar groups in isophorone. This displacement is an indication of the ionic nature of the compound; *i.e.*, the positive charge deshields the various protons to different extents.

Conductivity measurements on a 0.00528 N ethanolic solution corroborate the ionic structure; thus the equivalent conductivity is 335.2 ohm^{-1} cm^2. A similar solution of acetic acid would yield an equivalent conductivity of about 50 ohm^{-1} cm^2.

The experimental molecular weight of 3,3,5-trimethyl-2-cyclohexen-1-imine hydrothiocyanate as determined by vapor pressure osmometry in chloroform is 369,[6] compared with the calculated value of 196. Association of ionic species into ion pairs and ion multiplets to give high molecular values is not unusual.[7] On the other hand, titration of an aqueous solution of the thiocyanate with 0.1 N silver nitrate solution gave an equivalent weight of 196.

The ultraviolet spectrum observed in a 2.65×10^{-6} M methanolic solution showed one maximum, $\lambda_{\max}$ 258 mμ (ϵ 14.739). The application of Woodward's rules to isophorone leads to a predicted $\lambda_{\max}$ $(215 + 12 + 12) = 239$ mμ. The $\lambda_{\max}$ of the imine hydrothiocyanate indicates a conjugated structure. The shift is probably due to a greater resonance energy of the charged structure.

All these data are consistent with the formulation given above for the condensation of ammonium thiocyanate with a 3-substituted α,β-unsaturated cyclic ketone; *i.e.*, the reaction product is an imine hydrothiocyanate.

Experimental Section[8]

3,5,5-Trimethyl-2-cyclohexen-1-imine Hydrothiocyanate.—A mixture of 69 g (0.5 mole) of freshly distilled isophorone, 39.9 g (0.52 mole) of ammonium thiocyanate, 1.4 g of trisodium phosphate, and 30 ml of toluene was placed in a two-necked flask equipped with a mechanical stirrer and a Barrett-type water separator. The mixture was stirred and refluxed until the formation of water had ceased (3 hr). Excess toluene was removed, the residue was dissolved in chloroform, and the chloroform solution was filtered from the unreacted inorganic salts. After removal of the solvent, the residue (92 g, 92%) was crystallized from ethyl acetate yielding the pure yellow product (83.5 g, 85%) melting at 96–97°. The same yield could be obtained using sodium chloride and sodium sulfate instead of trisodium phosphate. Without the use of sodium salts, the yield of pure product was 57.5 g (60%). A sample for analysis prepared by a second crystallization from ethyl acetate showed the same melting point (96–97°).

Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.22; N, 14.27; S, 16.33. Found: C, 61.10; H, 8.25; N, 14.22; S, 16.39.

The picrate was prepared by combining a solution in ethanol of the imine hydrothiocyanate and an ethanolic solution of picric acid. After two crystallizations from ethanol it melted at 165–166°.

Anal. Calcd for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.10; H, 4.96; N, 15.23.

3-Methyl-2-cyclohexen-1-imine Hydrothiocyanate.—3-Methyl-2-cyclohexen-1-one was prepared according to the literature and distilled through a 30-cm Vigreux column.[9] A mixture of 22 g (0.20 mole) of 3-methyl-2-cyclohexen-1-one, 17 g (0.22 mole) of ammonium thiocyanate, 0.4 g of sodium dihydrogen phosphate, and 50 ml of toluene was stirred and refluxed until elimination of water was complete (2 hr). After treatment with chloroform—as described in the first case—the crude residue (30.5 g, 91%) was crystallized from a mixture of ethyl acetate and acetone giving 29.1 g (86.5%) of pure yellow product, mp 86–87°. After a second crystallization, the analytically pure imine hydrothiocyanate melted at 87–87.5°.

Anal. Calcd for $C_8H_{12}N_2S$: C, 57.10; H, 7.19; N, 16.65; S, 19.06. Found: C, 57.07; H, 7.14; N, 16.58; S, 19.13.

The picrate of this imine, after crystallization from ethanol, melted at 168–169°.

Anal. Calcd for $C_{13}H_{14}N_4O_7$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.12; H, 4.06; N, 16.50.

3,5-Dimethyl-2-cyclohexen-1-imine Hydrothiocyanate.—3,5-Dimethyl-2-cyclohexen-1-one was prepared according to the procedure of Horning, Denekas, and Field.[10] A mixture of 19 g (0.16 mole) of 3,5-dimethyl-2-cyclohexen-1-one, 12.5 g (0.165 mole) of ammonium thiocyanate, 0.4 g of sodium dihydrogenphosphate, and 50 ml of toluene was stirred and refluxed until elimination of water was complete (1.5 hr). After the removal of toluene and treatment of the residue with chloroform in order to remove the unreacted inorganic salts, the crude product (24.9 g, 89.5%) was obtained. One crystallization from ethyl acetate gave the product melting at 114–115° (23.5 g, 84.5%); after a second crystallization from ethyl acetate, the analytically pure imine hydrothiocyanate melted at 115–116°.

Anal. Calcd for $C_9H_{14}N_2S$: C, 59.43; H, 7.74; N, 15.37; S, 17.59. Found: C, 59.28; H, 7.82; N, 15.34; S, 17.53.

The picrate of this imine, after crystallization from ethanol, melted at 155–156°.

Anal. Calcd for $C_{14}H_{16}N_4O_7$: C, 47.73; H, 4.58; N, 15.90. Found: C, 47.68; H, 4.65; N, 16.01.

3-Phenyl-2-cyclohexen-1-imine Hydrothiocyanate.—3-Phenyl-2-cyclohexen-1-one was prepared following the procedure of Johnson, *et al.*[11] A mixture of 15.5 g (0.09 mole) of 3-phenyl-2-cyclohexen-1-one, 7.6 g (0.1 mole) of ammonium thiocyanate, 0.3 g of trisodium phosphate, and 50 ml of toluene was refluxed until no more water separated. The mixture was allowed to cool and the orange product was collected by filtration and washed with toluene. The filter cake was dissolved in chloroform, filtered from the unreacted inorganic salts, and concentrated to dryness to leave 19.2 g (92.5%) of crude product. A crystallization from acetone gave 16.9 g (81.5%) of the pure imine hydrothiocyanate, mp 134–135°. A sample for analysis, prepared by a second crystallization from acetone, melted at 134–135°.

Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.17; S, 13.91. Found: C, 67.80; H, 6.28; N, 12.13; S, 13.80.

The picrate of this imine after two crystallizations from ethanol melted at 195–196°.

Anal. Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00. Found: C, 54.11; H, 4.03; N, 13.95.

10-Methyl-1(9)-octalin-2-imine Hydrothiocyanate.—A mixture of 13.1 g (0.08 mole) of 10-methyl-1(9)-octalone-2, prepared according to the procedure of Marshall and Fanta,[12] 6.5 g (0.085 mole) of ammonium thiocyanate, 0.2 g of trisodium phosphate, and 30 ml of toluene was stirred and refluxed until no more water separated. After cooling, the orange product was collected by filtration. The filter cake was dissolved in chloroform, filtered from the unreacted inorganic salts, and concentrated to dryness to leave 15.5 g of crude product. A crystallization from a mixture of ethyl acetate and ethanol gave 14.4 g (82%) of the pure imine hydrothiocyanate, mp 114–116°. A simple for analy-

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[6] Average of two values.

[7] R. U. Bonnar, M. Dimbat, and F. H. Stross, "Number Average Molecular Weights," Interscience Publishers, Inc., New York, N. Y., 1958.

[8] Melting points are uncorrected.

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[11] W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).

[12] J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).

sis, prepared by a second crystallization from the same solvent mixture, melted at 115–116°.

Anal. Calcd for $C_{12}H_{18}N_2S$: C, 64.82; H, 8.16; N, 12.60; S, 14.42. Found: C, 64.74; H, 8.23; N, 12.55; S, 14.41.

The picrate of this imine after two crystallizations from ethanol melted at 154–155°.

Anal. Calcd for $C_{17}H_{20}N_4O_7$: C, 52.04; H, 5.14; N, 14.28. Found: C, 52.10; H, 5.25; N, 14.25.

2-Substituted-2-cyclohexen-1-imine Hydrothiocyanate.—2-Cyclohexen-1-one and carvone were treated, in refluxing toluene, with 1 mole equiv of ammonium thiocyanate as described above. One mole equivalent of water separated and oily imine hydrothiocyanates were formed. They could not be purified either by crystallization, distillation, or chromatography. They are yellow oils showing the three characteristic infrared peaks in the 2050–1610-cm^{-1} region, and are water soluble.

2-Phenyl-2-cyclohexen-1-one, prepared according to the literature[13] and treated with 1 mole equiv of ammonium thiocyanate in refluxing toluene, did not give any condensation product and was recovered unchanged from the toluene reaction mixture.

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Paracyclophane Phenols and Derivatives. I. The Synthesis and pK_A Values of 4-Hydroxy- and 4-Amino[2.2]paracyclophane

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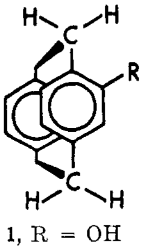
In connection with a continuing study of the Claisen rearrangement, we have had occasion to investigate the synthesis and reactivity of the phenol (1) and aromatic amine (2) derived from [2.2]paracyclophane. It soon became apparent that the chemical reactivity of these substituents was extensively modified by the uniquely strained nature of the aromatic ring to which they were attached.[2] In order to define these modified reactivities more quantitatively, the pK_A values of the phenol and the protonated amine (3) were determined, and are reported here. Since the general synthetic route used in this study varies extensively from other entries into this series,[3] the experimental details are reported in full.



1, R = OH
2, R = NH$_2$
3, R = NH$_3^+$

The pK_A measurements were made in an aqueous solution containing 5 wt % methanol. When compared to appropriate model compounds (Table I), these values reveal two major points: (1) the acid dissociation constant of the small linear substituent, OH,[4] on the [2.2]paracyclophane nucleus, primarily reflects the loss of resonance stabilization of the anion due to the bent nature of the adjacent benzene ring,[5] (2) the pK_A of the protonated anilium analog is apparently affected by at least two factors operating in opposite directions.[6]

TABLE I
pK_A VALUES

Compound	Solvent system[a]	pK_A	Ref
Phenol	H_2O	9.90	*b*
2,5-Dimethylphenol	H_2O	10.01	*b*
4-Hydroxy[2.2]paracyclophane	5% MeOH–H_2O	11.31	*c, d*
Aniline	H_2O	4.58	*e, f*
2,5-Dimethylaniline	H_2O	4.62	*e, f*
4-Amino[2.2]paracyclophane	5% MeOH–H_2O	4.43	*c, e, g*

[a] All measurements were made at 25.0°. [b] L. G. Hepler and W. F. O'Hara, *J. Phys. Chem.*, **65**, 811 (1961). [c] This work. [d] Range is 11.225–11.426; *n* is 7; one standard deviation is 0.08 pK_A unit. [e] Protonated form. [f] T. W. Zawidzki, H. M. Papeé, W. J. Canady, and K. J. Laidler, *Trans. Faraday Soc.*, **55**, 1738 (1959). [g] Range is 4.314–4.496; *n* is 9; one standard deviation is 0.04 pK_A unit.

Two major factors affecting the change in pK_A of the protonated 4-amino[2.2]paracyclophane relative to an appropriately substituted unstrained aniline are the change in resonance stabilization due to the bent nature of the adjacent benzene ring, and changes in steric factors influencing ion and molecule solvation.

An estimate of the change in resonance interaction can be made from the data on the paracyclophanol, since steric differences are minimized with this substituent.[4] This resonance effect, operating "normally" with planar benzene rings, acts to stabilize the neutral aniline molecule relative to the ion, and thus is a factor increasing the acidity of the conjugate acid. Since this effect is diminished by the paracyclophane geometry, the resonance effect in the [2.2]paracyclophane system leads to decreased acidity of the conjugate acid, relative to the model compound.

It has been observed, that the steric hinderance in amines such as 2-methyl- and 2,6-dimethylaniline[7a] and 2,4,6-tri-*t*-butylphenylhydrazine[7b,c] manifests itself through a destabilization of the solvation of the ionic

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