[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Application of Enamines to a New Synthesis of β-Ketonitriles

BY MARTIN E. KUEHNE

RECEIVED APRIL 22, 1959

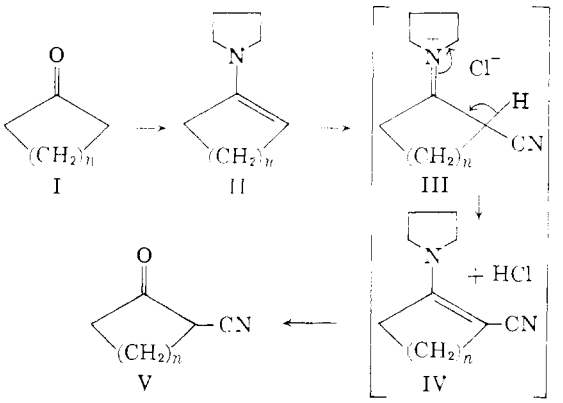
The ketones cyclopentanone through cyclononanone, 4-benzyloxycyclohexanone and 4-benzoyloxycyclohexanone were converted to their pyrrolidine enamines and these reacted with cyanogen chloride to give the corresponding α-cyanoketones. 2-Methylcyclohexanone yielded mainly 2-cyano-6-methylcyclohexanone and a small amount of 2-cyano-2-methylcyclohexanone. 2-Phenylcyclohexanone gave only 2-cyano-6-phenylcyclohexanone. The reaction was studied in different solvents, with and without the addition of triethylamine and with morpholine and piperidine enamines.

Alicyclic β-ketonitriles have been synthesized by base-catalyzed cyclization of dinitriles,[1,2] by condensation of cyclic ketones with formic esters followed by isoxazole formation with hydroxylamine and opening of the heterocycle with base,[3] or by chlorination of cyclic ketones and subsequent displacement with cyanide ion.[4] The first method is predominantly useful for the synthesis of the simplest homologous series of β-ketonitriles but cannot be generally applied to more complex cases where increasing substitution and dissymmetry will not only restrict the accessibility of the starting material but will also lead to mixtures of isomeric cyclization products. Syntheses through an isoxazole are restricted to ketones which bear no other functional groups sensitive to hot acid or to strong base. The third path is unsuitable in cases where the ketone incorporates centers which are competitively subject to halogenation, such as double bonds and aromatic substituents, especially if oxygenated, or where groups are present which are labile under the conditions of the displacement reaction.

In order to overcome these restrictions, a method was developed which permits the gentle and controlled introduction of a nitrile group α to a ketone, based on the Stork enamine synthesis.[5-7] The usefulness of the latter for C-alkylation and acylation of carbonyl compounds is becoming increasingly apparent.[8] Expanding this concept to the formation of β-ketonitriles, the homologus series of cyclic ketones from cyclopentanone to cyclononanone was converted to the respective enamines with pyrrolidine. These derivatives, listed in Table I, were treated with cyanogen chloride and the products hydrolyzed to the α-cyanoketones summarized in Table II. Extension of the series to cyclobutanone gave a mixture of materials which seemed to contain a small amount of the anticipated cyanocyclobutanone (see spectroscopic section), but a pure sample could not be obtained.

(1) S. T. Best and J. F. Thorpe, *J. Chem. Soc.*, **95**, 685 (1909).
(2) K. Ziegler, H. Eberle and H. Ohlinger, *Ann.*, **504**, 94 (1933).
(3) K. v. Auwers, Th. Bahr and E. Frese, *ibid.*, **441**, 68 (1925).
(4) R. E. Meyer, *Helv. Chim. Acta*, **16**, 1291 (1933).
(5) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).
(6) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128, 5129 (1956).
(7) H. K. Landesman, Ph.D. thesis, Columbia University, 1956.
(8) (a) S. Hünig, E. Benzig and E. Lücke, *Ber.*, **90**, 2833 (1957); **91**, 129 (1958); (b) L. Birkhofer and C. D. Barnikel, *ibid.*, **91**, 1996 (1958); (c) H. E. Baumgarten, P. L. Creger and C. E. Villars, THIS JOURNAL, **80**, 6609 (1958); (d) R. A. Benkeser, R. F. Lambert, P. W. Ryan and D. G. Stoffey, *ibid.*, **80**, 6573 (1958); (e) E. E. van Tamelen and S. Rosenberg Bach, *ibid.*, **80**, 3079 (1958); (f) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958); (g) R. B. G. Gabbard and E. V. Jensen, *ibid.*, **23**, 1406 (1958); (h) T. A. Crabb and K. Schofield, *J. Chem. Soc.*, 4276 (1958).

A brief consideration of the individual steps will clarify the usefulness and limitations of this sequence



In the basic medium, the initially formed immonium salt III rapidly looses a proton, activated by the adjacent nitrile and immonium functions, to give the new enamine IV. As part of a vinylogous cyanamide, the pyrrolidine nitrogen in IV is much less basic than that of the initial enamine II. Thus IV does not compete with II in the reaction with cyanogen chloride or with the HCl generated from the immonium salt III.[9] While this relationship blocks the formation of an undesired dinitrile, it also prevents complete utilization of the enamine II unless a further base such as triethylamine is added.

The presence of an additional base introduces a complication insofar as it may be expected to react with cyanogen chloride in competition with the enamine. Indeed, small amounts of diethylcyanamide were formed in the reaction of pyrrolidine enamines and triethylamine with cyanogen chloride. The extent of such competition cannot be predicted *a priori*. It will depend on the relative basicities of enamine and tertiary amine and be subject to steric factors in both compounds.

A demonstration of these effects is seen in the reaction of the pyrrolidine, piperidine and morpholine enamines of cyclohexanone and cyanogen chloride. In the presence of triethylamine, the respective yields of β-ketonitrile are 60, 19 and 6% with a corresponding increase in the formation of diethylcyanamide. While the basicity of N-alkylpyrrolidines and N-alkylpiperidines is the same (pK_a 10.2 – 10.7 in H_2O)[10,11] and normal

(9) The acyl enamines analogous to IV have, however, been reported to condense with an excess of acid chloride to give O-acyl derivatives.[8a]
(10) H. K. Hall, *J. Phys. Chem.*, **60**, 63 (1956).
(11) R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942).

TABLE I

ENAMINES OF CYCLIC KETONES

Enamine		Nitrogen, % Calcd.	Nitrogen, % Found	B.p. °C.	B.p. Mm.	$n^{20}D$[b]	Yield, %[a]
Cyclobutanone	$C_8H_{13}N$	...	...	74–76	11	....	
Cyclopentanone	$C_9H_{15}N$	10.20	10.48	85–86	10	1.5147	75
Cyclohexanone	$C_{10}H_{17}N$	9.26	9.53	92–93	5	1.5223	93
Cycloheptanone	$C_{11}H_{19}N$	8.47	8.46	100–102	5	1.5195	42
Cyclooctanone	$C_{12}H_{21}N$	7.81	7.99	113–114	5	1.5255	60
Cyclononanone	$C_{13}H_{23}N$	7.25	7.17	133–134	5	1.5270	72
2-Methylcyclohexanone	$C_{11}H_{19}N$	8.48	8.68	91–92	5	1.5145	53
2-Phenylcyclohexanone	$C_{16}H_{21}N$	6.16	5.83	125–126	0.005	1.5755	73

[a] Material distils only with extensive decomposition. [b] Refractive indexes may be used to indicate practical purity but are not indicative of absolute purity since all enamines still contained small amounts of ketone as seen by infrared absorption and turned yellow quickly in air as refractive indexes were taken, causing a drop in refractive index.

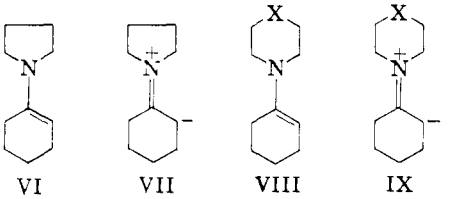
TABLE II

β-KETO NITRILES FROM PYRROLIDINE ENAMINES

		B.p. °C.	B.p. Mm.	$n^{20}D$ or M.p., °C.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Lit. ref.
2-Cyanocyclopentanone[a]	C_6H_7NO	125–126	10	1.4700	46	66.03	6.47	12.84	65.64	6.42	12.73	1
2-Cyanocyclohexanone[a]	C_7H_9NO	120–122	5	1.4775		Identical with material from 2-chlorocyclohexanone by infrared, $n^{20}D$ and b.p.						3,4
From pyrrolidine enamine[a]					60							
From pyrrolidine enamine[b]					(16)							
From piperidine enamine[a]					(19)							
From piperidine enamine[b]					(30)							
From morpholine enamine[a]					(6)							
From morpholine enamine[a,c]					(7)							
From morpholine enamine[b,c]					(24)							
2-Cyanocycloheptanone[a]	$C_8H_{11}NO$	131–132	10	1.4820	65	70.04	8.08	10.21	69.72	8.05	9.95	2
2-Cyanocyclooctanone[a]	$C_9H_{13}NO$	138–139	5	55–56	66	71.49	8.67	9.26	71.60	8.58	9.44	2
2-Cyanocyclononanone[a]	$C_{10}H_{15}NO$	129–130	3	44–45	77	72.69	9.15	8.48	72.35	9.17	8.69	
2-Cyano-6-methylcyclohexanone[a]	$C_8H_{11}NO$	139–140	14	1.4700	66	70.04	8.08	10.21	69.56	8.01	10.38	3
2-Cyano-6-phenylcyclohexanone[a]	$C_{13}H_{13}NO$	.....	..	137–141	67	78.36	6.58	7.03	78.07	6.74	7.08	

[a] With one equivalent triethylamine. [b] Without triethylamine. [c] In chloroform, otherwise all reactions in dioxane.

for tertiary amines, N-alkylmorpholines (pK_a 7.4 to 7.7 in H_2O) are less basic, though the difference in organic solvents is not as great as the respective basicities in water would indicate.[10] Thus the difference in reaction of piperidine and morpholine enamines, in competition with triethylamine, can be explained on the basis of their respective basicities but the difference between the piperidine and pyrrolidine enamines must be ascribed to a steric influence. Since these reactions proceed with precipitation of the products as insoluble salts and cleavage of a carbon–nitrogen bond in triethylamine, they are not equilibrium controlled and thus not controlled by the energy difference between the respective reactants and products but rather by the energy difference between the reactants and the transition state of the reaction. If one takes an association of cyanogen chloride or cyanogen chloride–triethylamine complex and the dipolar forms VII or IX of the enamines VI or VIII as the most general approximation of the transition state, then a comparison of the rates of reaction of pyrrolidine and piperidine enamines amounts to a comparison of the ease of formation of the dipolar structures VII and IX (see also ref. 7). From the generalization of Brown[12] the change of VI to VII would be favored over VIII to IX[13] and thus be in accord with the experimental observation.



VI VII VIII IX

In addition to electrophilic attack on carbon, one must also consider direct attack on the nitrogen of the enamine. In the reaction with cyanogen chloride, cleavage of the heterocycle would then be expected. While such products were not isolated, this may be the explanation for the difference from a theoretical 50% yield in the reactions without triethylamine.

The reaction of enamines with cyanogen chloride in the presence of triethylamine may be contrasted with their acylation. There Hünig[8a] obtained better yields of 2-acylcyclohexanones with morpholine and piperidine enamines than with pyrrolidine enamines. These reactions were done under reversible conditions and reflect the lesser ability of the acylating species to cleave a carbon–nitrogen bond in triethylamine.

The alkylation of α-monosubstituted ketones through enamine intermediates has been shown to take place at the α′-position[5] and to require more drastic conditions.[6] An inspection of molecular models of pyrrolidine enamines[14] has shown steric repulsion between the α-hydrogens of the amine ring and an equatorial α-substituent of the carbocyclic ring. Thus enamine formation will be

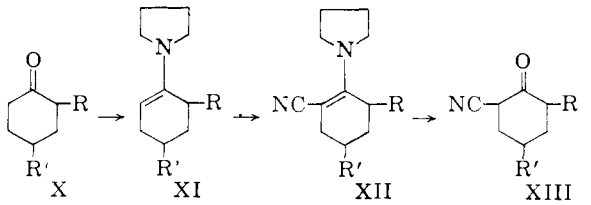
(12) H. C. Brown, J. H. Brewster and H. Schechter, THIS JOURNAL, **76**, 467 (1954).

(13) The extension from carbocyclic cases to a nitrogen heterocycle seems permissible since the unshared electron pair on nitrogen is considered to have special requirements comparable to a hydrogen atom; D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(14) W. R. W. Williamson, *Tetrahedron*, **3**, 314 (1958).

favored away from the substituent[6,7] and the substituent will be forced into an axial conformation and exert steric shielding of the α'-position of reaction. While 2-methylcyclohexanone enamine, in contrast to cyclohexanone enamine, does not react with methyl iodide in refluxing methanol,[6] an immediate reaction is found with cyanogen chloride at 5°, demonstrating the much smaller steric requirement of the electrophilic agent. 2-Cyano-6-methylcyclohexanone was obtained in the usual yield range (Table II). In addition 2% of material was obtained as forerun with a much lower boiling point (94–95°(14 mm.)) identical with that reported[3] for 2-cyano-2-methylcyclohexanone. The infrared absorption of this material confirmed the assignment of an unenolizable α-cyanoketone structure.

Since enamine formation with double bond direction toward an α-substituent is thus possible, it was thought that stabilization of the double bond by conjugation with an aromatic ring might facilitate the formation of this isomer. However, the pyrrolidine enamine of 2-phenylcyclohexanone lacked the intense ultraviolet maximum expected for a β-aminostyrene and on reaction with cyanogen chloride and hydrolysis gave the base-soluble 2-cyano-6-phenylcyclohexanone (XIIIb) as sole product. In this instance the intermediate cyano enamine XIIb was isolated, purified and then hydrolyzed to the β-ketonitrile.



X XI XII XIII

a, R = CH_3, R' = H; b, R = C_6H_5, R' = H; c, R = H, R' = $OCOC_6H_5$; d, R = H, R' = $OCH_2C_6H_4$.

In order to determine the magnitude of solvent effects, the pyrrolidine enamine of 4-benzoyloxycyclohexanone (XIc) was treated with cyanogen chloride in a variety of solvents. Table III summarizes the yields of product XIIIc and recovered starting material Xc.

TABLE III

COMPARISON OF SOLVENTS FOR REACTION OF 4-BENZOYLOXY-1-PYRROLIDINOCYCLOHEXENE WITH CYANOGEN CHLORIDE WITHOUT TRIETHYLAMINE

Solvent	Yield keto nitrile, %	Yield recovered ketone, %
Dioxane–ether (1:1)	21	48
Dioxane	37	48
Dimethylformamide	12	27
Chloroform	2	37
Methanol	10	60
Tetrahydrofuran	15	50
1,2-Dimethoxyethane	27	..

The principal limitation of the new reaction sequence is in the formation of certain of the enamine intermediates. Using benzene for azeotropic removal of water, this process could not be driven to completion in some cases, as seen by the extent of water separation (see Experimental section, general procedure), by the amounts of recovered starting components on distillation and from infrared spectra of the reaction mixtures (ketone band 1780–1695 cm.$^{-1}$, enamine band 1640–1630 cm.$^{-1}$). Thus in the worst instance, the enamine formation of cycloheptanone and pyrrolidine appears to stop at 42%.[15]

Spectral Data.—Table IV demonstrates the shift of carbonyl absorption of cyclic ketones by α-cyano substitution, analogous to the shift observed with equatorial α-bromoketones. In addition to nitrile absorption at 2260 cm.$^{-1}$, a much smaller peak was seen at 2210–2220 cm.$^{-1}$ which is ascribed to the enolic form of the compounds. In 2-cyanocyclooctanone this absorption decreased markedly and in 2-cyanocyclononanone only a trace of absorption was visible. In Nujol, 2-cyanocycloöctanone, 2-cyanocyclononanone and 2-cyano-6-phenylcyclohexanone gave only one nitrile band at 2255 cm.$^{-1}$ and carbonyl absorption at 1710 cm.$^{-1}$.

The cyano enamine precursors of 2-cyano-6-phenylcyclohexanone, 2-cyanocycloöctanone and nonanone (XIIb, IV, n = 5,6) showed strong maxima at 2170–2180 cm.$^{-1}$ (NC=**CCN**) and 1570–1580 cm.$^{-1}$ (**NC**=CCN). The enamines of all parent ketones absorbed at 1630–1640 cm.$^{-1}$ (NC=C).

TABLE IV

INFRARED ABSORPTION OF α-CYANOKETONES AND PARENT KETONES IN CM.$^{-1}$ ($CHCl_3$)

n	RCHCO—CCN (CH_2)$_n$	—COCCN OH R' CH=CCN	C=O	C=O parent ketone
1	R = R' = H	2260(?) ?	1805(?)	1780
2	R = R' = H	2260 2220	1760	1735
3	R = R' = H	2265 2215	1735	1710
3	R = CH_3, R' = H	2260 2215	1730	1710
3	R = H, R' = CH_3	2275 ..	1735	1710
3	R = C_6H_5, R' = H	2265 2215	1735	1710
4	R = R' = H	2260 2220	1725	1705
5	R = R' = H	2260 2210	1720	1695
6	R = R' = H	2255 (2210)	1720	1695

In addition to providing a mild method for the conversion of cyclic ketones to the corresponding α-cyanoketones, the present process compares favorably in yield and operational ease[16] with the established sequences. Thus 2-cyanocyclohexanone was prepared in 56% over-all yield through the pyrrolidine enamine and in 50% yield through the α-chloroketone (reported[4] 64% yield). 4-Benzyloxycyclohexanone was converted to the α-cyanoketone XIIId in 24% over-all yield through the isoxazole and in 55% yield through the enamine.

Acknowledgment.—The author thanks the Analytical Research Section for elemental analyses and infrared spectra and especially for the rapid and competent processing of the unstable enamines. Miss Olive Reynolds gave valuable assistance in the laboratory.

(15) Using toluene as solvent, good yields of this enamine can be obtained; G. Stork and A. Brizzolara, private communication.

(16) Cyanogen chloride was prepared according to "Inorganic Syntheses," Vol. II, first ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 91, and can now be purchased from Imperial Chemical Industries, Ltd., London, S. W. 1, England.

Experimental Section

General Procedure.—Nitrogen was passed through a solution of 1.0 mole of the respective cyclic ketone, 75 g. (1.05 moles) of pyrrolidine and a few crystals of *p*-toluenesulfonic acid in 375 ml. of benzene. The reaction was then refluxed under nitrogen, using a water trap, until separation of water had stopped. (Cyclobutanone, 5 hours, 16 ml.; cyclopentanone, 2.5 hours, 19 ml.; cyclohexanone, 3 hours, 19 ml.; cycloheptanone, 20 hours, 10 ml.; cycloöctanone, 20 hours, 11 ml.; cyclononanone, 18 hours, 19 ml.; 2-methylcyclohexanone, 40 hours, 12 ml.; 2-phenylcyclohexanone, 20 hours, 14 ml.) The benzene was then distilled slowly and the residue distilled *in vacuo* giving the enamines described in Table I.

The distilled enamine (0.40 mole) and 41 g. (0.41 mole) of triethylamine were dissolved in 500 ml. of dioxane, distilled from sodium, and 25 g. (0.41 mole) of cyanogen chloride in 70 g. of dioxane added in a slow stream, with stirring in a salt–ice-bath, keeping the strongly exothermic reaction at 3–8°. The reaction was kept at 3–6° for an additional 2 hours, overnight at room temperature and finally poured into 3 l. of ice and water. The mixture was acidified to congo with 10% hydrochloric acid, 250 ml. of ether added and shaken for 20 minutes. During this time additional acid had to be added periodically to maintain the acidicity. After 5 additional short extractions with ether, the combined extracts were washed with water and saturated salt solution, dried over magnesium sulfate and evaporated *in vacuo*. After 4 hours the aqueous portion was again extracted with ether and the small amount of additional product obtained from these extracts combined with the major portion.

Distillation yielded the cyanoketones described in Table II. Notes: (1) The enamine formation was carried out on 0.25 mole with cyclobutanone, 0.60 mole with cycloöctanone, 0.10 mole with cyclononanone and 2-phenylcyclohexanone. Cyanogen chloride additions were carried out on a smaller scale corresponding to the respective yields of the enamines. The data in the general procedure above has been given as extrapolations in these instances. (2) The enamine of cyclobutanone decomposes on distillation at 74–76° (11 mm.) and was thus used without purification. (3) The crude reaction product from the cyclobutanone enamine showed infrared absorption at 1805 cm.$^{-1}$ med. (2-cyanocyclobutanone carbonyl), 2220 str. (diethylcyanamide nitrile), 2260 shld. (alkyl nitrile). On distillaton only diethylcyanamide, little high molecular weight material and resin were obtained.

(4) On distillation of the crude 2-cyanocycloöctanone, 61% (41 g.) of the distillate was collected at 138–139° (5 mm.) and 39% (15.9 g.) at 146–152° (0.5 mm). The lower boiling fraction was recrystallized from benzene–heptane to give 36 g. of product, m.p. 54–56°. The higher boiling enamine nitrile was heated for 15 minutes with stirring on a steam-bath with 70 ml. of 3% hydrochloric acid. After cooling, extraction with ether, concentration and recrystallization, 9.3 g. of additional keto nitrile was obtained.

(5) The initially extracted crude mixture of 2-cyanocyclononanone and the corresponding enamine nitrile was heated directly with an excess of 3% hydrochloric acid, extracted with ether and the extract concentrated and distilled.

(6) From 2-phenylcyclohexanone, the cyano enamine was obtained as the main product on evaporation of the ether extracts. Trituration of the reaction product with a small amount of ether gave a 67% yield (15.7 g.) of this compound, m.p. 108–113°, recrystallized from ethanol m.p. 115–116°; ultraviolet in ethanol λ_{max} 289 mμ, ε 17470.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.01; H, 7.99; N, 11.10. Found: C, 81.48; H, 7.94; N, 10.89.

Evaporation of the ether mother liquor from trituration gave 0.8% (0.2 g.) of the β-keto nitrile, m.p. 137–141°, described in Table II.

(7) The 2-phenylcyclohexanone, m.p. 55°,[17,18] was purified through the oxime, m.p. 173°.[18]

2-Cyano-6-phenylcyclohexanone (XIIIb).—A suspension of 1.0 g. (0.004 mole) of the cyano enamine XIIb in 20 ml. of 3% hydrochloric acid was refluxed for 30 minutes with stirring. The new suspension was cooled, filtered and washed with water to give 0.79 g. of product (100% yield) which could be recrystallized from ethanol. Several recrystallizations did not alter the melting point or restrict its range of 137–141°, suggesting ready epimerization between *cis* and *trans* forms; though the former presumably predominates.

4-Benzoyloxy-2-cyanocyclohexanone (XIIIc).—Comparison of solvents for reaction of enamines with cyanogen chloride: Solutions of 6.0 g. (0.027 mole) of 4-benzoyloxycyclohexanone (Xc) and 2.0 g. (0.028 mole) of pyrrolidine in 60 ml. of benzene were refluxed under nitrogen for 3 hours with an azeotropic water separator. The benzene was removed *in vacuo* and the enamine, m.p. 133–136°, dissolved without purification in the freshly dried solvents indicated below. When necessary, the mixtures were warmed briefly to ensure solution and all were cooled in a Dry Ice–acetone-bath. With rapid stirring a solution of 1.8 g. (0.029 mole) of cyanogen chloride in 8 ml. of dry ether was then added in one portion, stirring continued 1 hour with ice cooling and 15 hours at room temperature. After addition of 200 ml. of ice-water, acidification to *p*H 4 and addition of 100 ml. of methylene chloride, the mixtures were shaken for 15 minutes, separated and extracted twice more with methylene chloride. The combined methylene chloride solutions were washed with water and extracted with five 100-ml. portions of iced 5% KOH. Acidification to *p*H 4, extraction with methylene chloride, drying and evaporation gave the crystalline β-ketonitrile, m.p. 122–125°, in the quantities indicated. Evaporation of the initial methylene chloride extracts and crystallization from ether–ligroin gave recovered 4-benzoyloxycyclohexanone: a, 50 ml. of dioxane and 50 ml. of ether, 1.4 g. (2.9 g. recov.); b, 75 ml. of dioxane, 2.5 g. (2.9 g. recov.); c, 100 ml. of dimethylformamide, 0.80 g. (1.60 g. recov.); d, 100 ml. of chloroform, 0.14 g. (2.2 g. recov.); e, 100 ml. of methanol, 0.70 g. (3.6 g. recov.); f, 100 ml. of tetrahydrofuran, 1.0 g. (3.0 g. recov.); g, 100 ml. of 1,2-dimethoxyethane, 1.8 g. Note: When dioxane was used, the solution was supercooled and CNCl added before crystallization of the solvent occurred. When methanol was used only part of the enamine was initially in solution but all dissolved on addition of CNCl.

Repeating the reaction in dioxane (b) on a tenfold scale several times gave the same yield of product. Variation of the amount of CNCl in b to 0.65 equivalent (0.017 mole) or 1.6 equivalents (0.043 mole) did not alter the yield.

The β-ketonitrile was recrystallized from methylene chloride–benzene to m.p. 124–125°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.96; H, 5.58; N, 5.77.

4-Benzyloxy-2-cyanocyclohexanone (XIIId). a.—Under a nitrogen atmosphere sodium methoxide, prepared from 10.0 g. (0.43 mole) of sodium and dried for 2 hours at 150° (0.01 mm.), was added to a solution of 30.0 g. (0.15 mole) of 4-benzyloxycyclohexanone (Xd)[19] in 100 ml. of dry benzene. After stirring for 5 minutes, a solution of 56.0 g. (0.76 mole) of freshly distilled ethyl formate in 200 ml. of dry benzene was added in a slow stream with rapid stirring and cooling in ice. The mixture was stirred for 20 hours at room temperature, then poured into 200 ml. of ice-water and extracted thoroughly. After an additional five extractions with 100-ml. portions of 0.5% KOH, the combined basic solutions were acidified to *p*H 4 with iced 10% hydrochloric acid and extracted thoroughly with methylene chloride, giving 31.0 g. (91% yield) of crude formyl ketone as a heavy oil which was used directly in the next step.

A solution of 31.0 g. (0.13 mole) of the formyl ketone in 500 ml. of glacial acetic acid was stirred with 10.1 g. (0.14 mole) of powdered hydroxylamine hydrochloride for 100 minutes on a steam-bath. The acetic acid was removed at 60° *in vacuo*, the residue taken up in benzene and poured onto a column of 150 g. of Florex. Elution with 5% methylene chloride in benzene, repeated washing of the combined eluate with iced 0.5% KOH solution, drying and evaporation gave 20.0 g. (66% yield) of crude isoxazole as an oil which was converted directly to the β-ketonitrile.

The crude isoxazole (0.087 mole) was dissolved in 350 ml. of dry benzene and added to a solution of 3.5 g. (0.15 mole) of sodium in 90 ml. of methanol. After stirring for 20 minutes at room temperature the mixture was poured into 300 ml. of ice-water and extracted thoroughly. Further extraction with 5 iced portions of 100 ml. of 0.5% KOH, acidification of the combined basic solutions to *p*H 4 and thorough

(17) M. S. Newman and M. D. Farbman, THIS JOURNAL, **66**, 1550 (1944).

(18) J. v. Braun, H. Gruber and G. Kirschbaum, *Ber.*, **55**, 3668 (1922).

(19) D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957).

extraction with methylene chloride gave the ketonitrile as a pale yellow oil. Distillation from an oil-jacketed flask at 170° (0.001 mm.) gave 8.2 g. (41% yield) of product; 24% yield over-all from 4-benzyloxycyclohexanone; 2,4-dinitrophenylhydrazone, m.p. 161–162°.

Anal. Calcd. for $C_{20}H_{19}N_5O_5$: C, 58.67; H, 4.68; N, 17.11. Found: C, 59.02; H, 4.83; N, 17.24.

b.—A solution of 6.0 g. (0.029 mole) of 4-benzyloxycyclohexanone and 3.0 g. (0.042 mole) of pyrrolidine in 60 ml. of benzene was refluxed under nitrogen with an azeotropic water separator for 4 hours. The benzene and excess pyrrolidine were then removed *in vacuo* and the residual enamine dissolved in 50 ml. of dry dioxane. The solution was stirred in an ice-bath and a solution of 1.9 g. (0.031 mole) of cyanogen chloride in 8 ml. of dry ether was added in one portion. After stirring the suspension for 3 hours in the cold, followed by gradual warming to room temperature, it was poured into 300 ml. of ice-water and 200 ml. of methylene chloride. After acidification to *p*H 4 the mixture was shaken for 20 minutes, separated and extracted twice more with methylene chloride. The combined methylene chloride solution was extracted 6 times with 100-ml. portions of iced 0.5% KOH, the combined basic solutions acidified to *p*H 4 and extracted thoroughly with methylene chloride. Evaporation and distillation as under a gave 1.7 g. (25% yield) of product with an infrared spectrum identical with that of the material under a. Repeating the reaction with 2.9 g. (0.029 mole) of triethylamine added to the enamine solution gave 3.7 g. (55% yield) of product.

SUMMIT, N. J.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

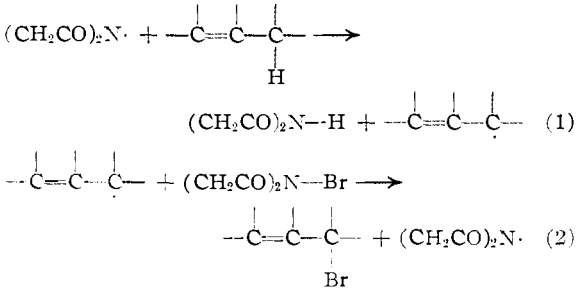
N-Bromosuccinimide. III. Stereochemical Course of Benzylic Bromination[1]

BY HYP J. DAUBEN, JR., AND LAYTON L. MCCOY[2]

RECEIVED APRIL 6, 1959

While the general radical-chain nature of the allylic bromination reaction of alkenes by NBS is now well established, details of the mechanism such as the degree of freedom and the stereoconfiguration of the intermediate radical are not known. Use of the criteria of double bond migration (formation of isomeric allylic bromides) and of geometrical isomerization about the double bond in the reaction of alkenes with NBS has failed to provide conclusive evidence on these points. The present study utilizes a third criterion, stereochemical course with an optically-active reactant, for this purpose. (−)-α-Deuterioethylbenzene, prepared by the method of Eliel, has been shown to react with NBS in refluxing carbon tetrachloride with benzoyl peroxide initiation to produce phenylmethylcarbinyl bromide with at least 99.7% racemization. Since (+)-phenylmethylcarbinyl bromide has been found to be configurationally stable under the reaction and work-up conditions, this result is consonant only with the interpretation that the benzylic bromination reaction involves a completely free α-phenethyl radical intermediate that undergoes racemization at least 600 times faster than it displaces on NBS.

Considerable evidence has accumulated, since the discovery of the reaction by Ziegler and co-workers,[3] that the N-bromosuccinimide (NBS) reacts with alkenes to form allylic bromide products by a radical chain mechanism involving initiation by various radical sources and propagation by steps 1 and 2.[4] Certain other aspects of the reaction, formation of isomeric allylic bromide products, geometrical isomerization about the double bond during the reaction and stereochemical course of the substitution, also have important bearing on more intimate details of the reaction mechanism, particularly in establishing the degree of freedom and the configuration of the intermediate allylic radical.



Formation of a free allylic radical intermediate in the reaction of an alkene with NBS would be expected to lead to the formation of the two possible isomeric allylic bromide products (neglecting, for the present, geometrical isomers). In a number of cases (mainly 1-alkenes) mixtures of the isomeric allyl bromides have been shown to be formed, and in some other cases the only isolable allylic bromide product has been found to possess the isomerized structure.[5] While such observations might be regarded as evidence for a mesomeric free radical intermediate, Bateman and co-workers[6] have pointed out that this conclusion is justified only if it has been demonstrated that the isomeric allylic bromide products have been formed in kinetically-controlled, not thermodynamically-controlled, proportions. Since, in the only cases so far examined, these same workers[6] have shown that the mixtures of allylic bromides formed from the reaction with NBS are the same as those produced by thermal equilibrization of similar allylic bromides, it is obvious that the allylic isomerization criterion has not yet provided convincing evidence of a free radical intermediate in the NBS reaction.

The occurrence of geometrical isomerization during the reaction of NBS with the less stable alkene isomer would also indicate a mesomeric free radical

(1) (a) Taken from the Ph.D. Thesis of Layton L. McCoy, University of Washington, 1951. (b) Supported in part by research contract No. N8-onr-52007 with the Office of Naval Research, U. S. Navy.

(2) Predoctoral Fellow, Atomic Energy Commission, 1950–1951.

(3) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(4) For a recent summary of evidence and pertinent references; see H. J. Dauben, Jr., and L. L. McCoy, THIS JOURNAL, **81**, 4863 (1959).

(5) References given in: (a) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948); (b) T. D. Waugh, "NBS, Its Reactions and Uses," Arapahoe Chemicals, Inc., Boulder, Colo., 1951; (c) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 381–386. The report of F. L. Greenwood and M. D. Kellert (THIS JOURNAL, **78**, 4842 (1953)) that 2-heptene with NBS gave only 4-bromo-2-heptene apparently represents the only case in which a single unisomerized allylic bromide has been formed when isomeric allylic bromide products would have been expected.

(6) L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 941 (1950); L. Bateman, J. I. Cunneen, J. M. Fabian and H. P. Koch, *ibid.*, 936 (1950).