Epoxyamines. II. Synthesis, Reactions, and Rearrangement[1]

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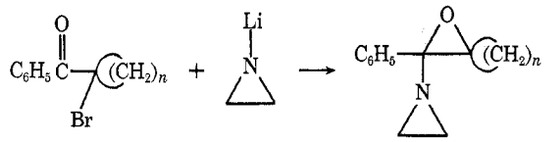
Received August 6, 1971

Treatment of the lithium salt of ethylenimine on α-bromocyclohexyl phenyl ketone yields 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (**3**), the first epoxyamine ever to be isolated and characterized. Reactions of this compound with dilute hydrochloric acid, sodium borohydride, methanol, benzoic acid, and organolithium compounds are discussed in detail. When heated to reflux temperature in *o*-dichlorobenzene for 15 hr under a nitrogen atmosphere, the epoxyamine rearranges with ring expansion to give 2-(1-aziridinyl)-2-phenylcycloheptanone (**17**) and not to the expected α-(1-arizidinyl)cyclohexyl phenyl ketone (**19**). The structure of the rearrangement product is established both by synthetic and by degradative studies.

Ethylenimine is known to differ from other cyclic and acyclic secondary amines in its reaction with carbonyl compounds.[3,4] Thus aliphatic aldehydes and ketones react with ethylenimine in equimolar quantities, yielding stable aminohydrines which are generally unknown with other amines. This unusual reactivity of ethylenimine prompted a study of the reactions of its lithium salt on α-bromo ketones as part of a general investigation of the reaction of α-halo ketones with various nucleophiles.

Treatment of α-bromocyclohexyl phenyl ketone (**1**) with the lithium salt of ethylenimine in ether at room temperature gave 65–78% of a material which was subsequently shown to be an epoxyamine, 2-(1-aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (**3**) on the basis of its elemental analysis, spectral data, and chemical reactions. The infrared spectrum of **3** did not show any hydroxyl or carbonyl absorptions, but had strong peaks at 1025 and 1045 cm^{-1} indicative of an ether linkage. The nmr spectrum was consistent with the structure, showing aromatic protons from τ 2.45 to 2.85 and the saturated ring protons from τ 7.8 to 9.0 in the ratio 5:14. The reaction of α-bromocyclopentyl phenyl ketone (**2**) with the lithium salt of ethylenimine proceeded in the same manner, yielding the epoxyamine, 2-(1-aziridinyl)-2-phenyl-1-oxaspiro-[2.5]heptane (**4**).[5]

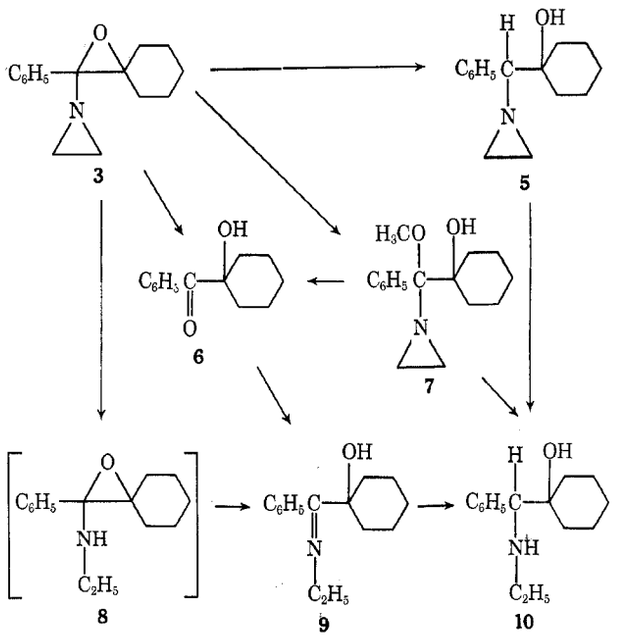


1, $n = 5$ **3**, $n = 5$
2, $n = 4$ **4**, $n = 4$

Reactions.—Epoxyamines are very susceptible to acid hydrolysis. Thus on treatment with dilute hydrochloric acid, **3** was rapidly hydrolyzed to the known α-hydroxycyclohexyl phenyl ketone[6] (**6**) in 90% yield. Reduction of **3** with sodium borohydride in methanol at room temperature gave 75% of 1-(α-1-aziridinylbenzyl)cyclohexanol (**5**). The fact that the aziridine ring was not cleaved with sodium borohydride is in agreement with previous findings.[7] Also the direction of the opening of the epoxide ring with hydride ion is the same as in the reduction of epoxy ethers with lithium aluminum hydride.[8]

Catalytic hydrogenation of the aziridinyl alcohol **5** in ethanol at atmospheric pressure in the presence of 10% palladium on carbon opened the aziridine ring[9] to give 85% of 1-(α-*N*-ethylaminobenzyl)cyclohexanol (**10**) characterized as its hydrochloride. Amino alcohol **10** was also formed in 80% yield by the direct hydrogenation of **3** in methanol using the same catalyst. The first step in this reduction is probably hydrogenolysis of the aziridine ring to the intermediate epoxyamine **8**, compounds of which type are known to rearrange rapidly to the α-hydroxyimines.[10] α-Hydroxycyclohexyl phenyl ketone *N*-ethylimine (**9**) thus formed would be reduced under the hydrogenation conditions to give the amino alcohol **10**. Hydroxyimine **9** was synthesized by heating a mixture of hydroxy ketone **6** and ethylamine in a sealed tube in the presence of potassium carbonate as a dehydrating agent. This imine **9** was reduced with sodium borohydride in methanol to give 85% of **10** identical in all respects with the hydrogenation products of **3** and **5**.

Epoxyamine **3** reacted with methanol in the presence



(1) Paper I in this series: C. L. Stevens and P. M. Pillai, *J. Amer. Chem. Soc.*, **89**, 3084 (1967).

(2) Abstracted in part from the Ph.D. dissertation of P. M. Pillai, Wayne State University, 1968; Frank Knoller Predoctoral Fellow, 1966–1967.

(3) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 464 (1949).

(4) W. J. Rabourn and W. L. Howard, *J. Org. Chem.*, **27**, 1039 (1962).

(5) C. L. Stevens, T. R. Potts, and P. M. Pillai, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, P-25.

(6) C. L. Stevens and E. Farkas, *J. Amer. Chem. Soc.*, **74**, 618 (1952).

(7) C. L. Stevens, M. E. Munk, C. H. Chang, K. G. Taylor, and A. L. Schy, *J. Org. Chem.*, **29**, 314 (1964).

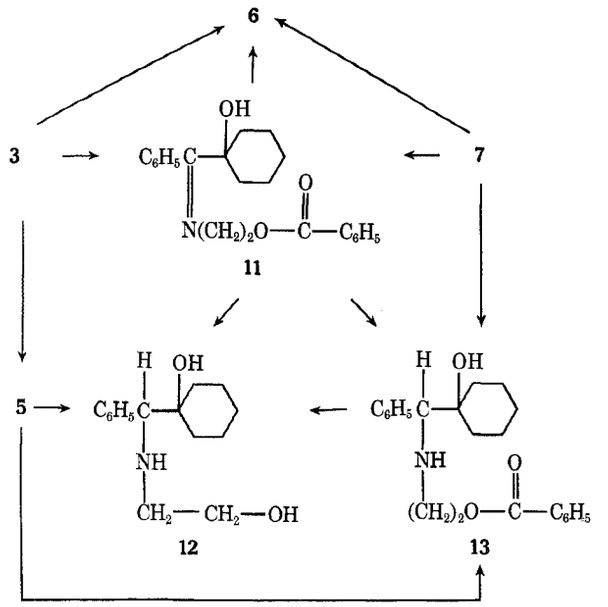
(8) C. L. Stevens and T. H. Coffield, *J. Amer. Chem. Soc.*, **80**, 1919 (1958).

(9) Hydrogenation of ethylenimines to ethylamines is well established. See ref 7 and also M. Kharasch and H. Priestly, *J. Amer. Chem. Soc.*, **61**, 3425 (1939).

(10) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).

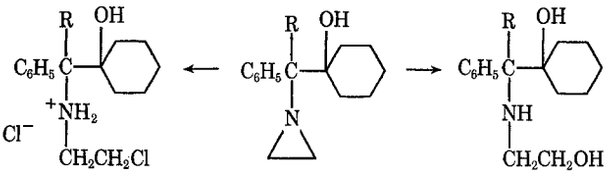
of a trace of hydrogen chloride to give 1-(α-1-aziridinyl-α-methoxybenzyl)cyclohexanol (**7**) in 78% yield. In this reaction, epoxyamines closely resemble epoxy ethers which form α-hydroxy ketals under the same conditions.[6] The infrared spectrum of **7** indicated the presence of a hydroxyl group and the nmr spectrum showed that an aziridine ring was present in the molecule. The structure of **7** was further confirmed by its hydrolysis with dilute hydrochloric acid to the α-hydroxy ketone **6** and also by the formation of amino alcohol **10** when **7** was hydrogenated in the presence of 10% palladium on carbon as catalyst.

Treatment of epoxyamine **3** with an equivalent amount of benzoic acid in refluxing hexane opened the epoxide and aziridine rings to give 70% of α-hydroxycyclohexyl phenyl ketone *N*-(2-benzoyloxyethyl)imine (**11**). Acid hydrolysis of **11** to the α-hydroxy ketone **6** showed the position of the C=N bond in the molecule. Formation of **11** in 60% yield by the reaction of benzoic acid with **7** in refluxing benzene provides further evidence for the structure of **11**. Treatment of the imino ester **11** with sodium borohydride not only reduced the imine function in the molecule but also cleaved the ester group to give 1-(α-2-hydroxyethylaminobenzyl)cyclohexanol (**12**) in 63% yield. Compound **12** was also prepared by heating the aziridinyl



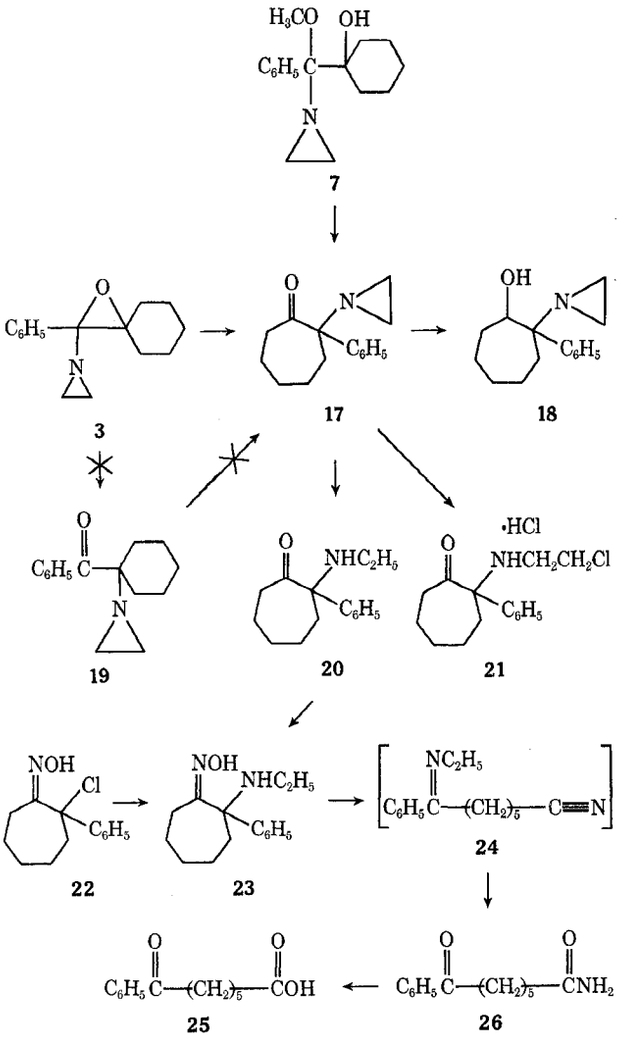
alcohol **5** with 1 *N* perchloric acid according to a procedure previously reported.[7] Reduction of the imine without cleavage of the ester group was accomplished by catalytic hydrogenation in the presence of 10% palladium on carbon to yield 1-(α-2-benzoyloxyethylaminobenzyl)cyclohexanol (**13**). Compound **13** was also prepared by refluxing equimolar quantities of aziridinyl alcohol **5** and benzoic acid in benzene. The ester group in **13** was hydrolyzed with aqueous alcoholic sodium hydroxide to give 88% of **12**.

Treatment of the epoxyamine with both methyllithium and phenyllithium opened the epoxide ring in a way analogous to the reaction of Grignard reagents with epoxy ethers.[11] The aziridinyl alcohols (**15**) thus formed were treated with hydrogen chloride in ethyl acetate to give the 2-chloroethylamino derivatives as their hydrochlorides. The aziridine ring was also opened by heating **15** with 1 *N* perchloric acid to yield the amino diols **16**.



14a, R = CH_3 **15a**, R = CH_3 **16a**, R = CH_3
b, R = C_6H_5 **b**, R = C_6H_5 **b**, R = C_6H_5

Rearrangement.—When heated to the reflux temperature in *o*-dichlorobenzene for 15 hr under a nitrogen atmosphere, epoxyamine **3** rearranged with ring expansion to give 2-(1-aziridinyl)-2-phenylcycloheptanone (**17**) in 30–40% yield, the remainder of the material being an intractable resin.[12] Although the direction of the epoxide ring opening in this rearrangement is in agreement with the acid-catalyzed rearrangement of epoxy ethers,[13] it does not conform to a previous postulate by Kirmann[14] which would predict the formation of α-(1-aziridinyl) cyclohexyl phenyl ketone (**19**) as the rearrangement product. Studies on an-



(11) C. L. Stevens and W. Holland, *J. Org. Chem.*, **23**, 781 (1958).

(12) Epoxyamine **3** polymerizes slowly at room temperature and rapidly if heated without a solvent.

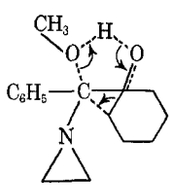
(13) C. L. Stevens and S. J. Dykstra, *J. Amer. Chem. Soc.*, **76**, 4402 (1954).

(14) A. Kirmann, R. Muths, and J-J. Richl, *Bull. Soc. Chim. Fr.*, 1469 (1958).

other epoxyamine indicate[5] that the direction of this rearrangement is general in the case of epoxyamines with an aziridinyl group. The direction of the rearrangement and the stability of the epoxyamine are probably controlled by the steric requirements of the lone pair of electrons on the nitrogen.[15]

In order to show that the conjugated amino ketone **19** was not an intermediate in this transformation of **3** to **17**, **19** was prepared by the general method[7,16] involving the action of ethylenimine on the epoxy ether, 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane.[6] After **19** was subjected to the same rearrangement conditions, most of the starting material was recovered unchanged and an examination of the infrared spectrum of the crude reaction mixture provided evidence that no detectable amount of **17** was formed.

The rearranged amino ketone **17** was also formed in 40% yield when **7** was heated at 180° in *o*-dichlorobenzene under a nitrogen atmosphere for 24 hr. The formation of **17** from **7** can be envisaged as proceeding through the intermediate epoxyamine or through a six-membered ring cyclic transition state **27**. However,



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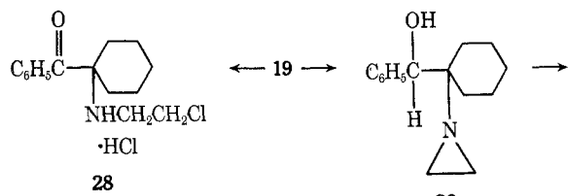
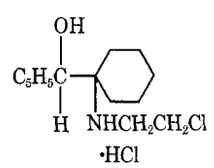
the experimental data available are not sufficient to differentiate between the two mechanistic pathways.

Amino ketone **17** was further characterized by its reduction with sodium borohydride in methanol to 2-(1-aziridinyl)-2-phenylcycloheptanol (**18**) and by its reaction with an excess of hydrogen chloride in ethyl acetate to give 2-(2-chloroethyl)amino-2-phenylcycloheptanone hydrochloride (**21**). Upon catalytic hydrogenation in ethyl acetate at atmospheric pressure in the presence of 10% palladium on carbon, **17** was selectively reduced to 2-*N*-ethylamino-2-phenylcycloheptanone (**20**) characterized as its hydrochloride. Amino ketone **20** was converted to the corresponding oxime, **23**, by treating it with hydroxylamine hydrochloride in alcohol in the presence of pyridine. Synthesis of **23** was also achieved by the action of ethylamine on the known 2-chloro-2-phenylcycloheptanone oxime.[17] The structure of the amino ketone oxime **23** was further confirmed by the formation of 6-benzoylhexanamide (**26**) when the oxime was subjected to Beckmann degradation conditions using polyphosphoric acid.[18] The conversion of **23** to **26** by this second-order Beckmann reaction can be explained as taking place through the intermediate formation of iminonitrile **24**, which would then be hydrolyzed to the ketoamide under the experimental conditions.[19] On treatment with aqueous alcoholic sodium hydroxide, **26** was hydrolyzed to the known 6-benzoylhexanoic acid[20] (**25**), the identity of which was established by direct comparison with an authentic sample.

The α-aziridinyl ketone **19** was further characterized by treating it with an excess of hydrogen chloride in ethyl acetate to give α-*N*-(2-chloroethylamino)cyclohexyl phenyl ketone hydrochloride (**28**). Also reduction of **19** with sodium borohydride in methanol gave the amino alcohol **29**.



28 **29**



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Treatment of **29** with hydrogen chloride in ethyl acetate afforded 1-(2-chloroethyl)amino-1-α-hydroxylbenzylcyclohexane hydrochloride (**30**).

Experimental Section[21]

2-(1-Aziridinyl)-2-phenyl-1-oxaspiro[2.5]octane (3).—A 500-ml three-necked round-bottomed flask was fitted with a mechanical stirrer, an efficient water condenser, and a dropping funnel. The entire system was flushed with dry nitrogen and a steady nitrogen atmosphere was maintained. Freshly distilled ethylenimine[22] (3.9 g, 90 mmol) dissolved in 100 ml of dry ether was transferred into the flask. A solution of 1.6 *M* *n*-butyllithium[23] in hexane (28 ml, 45 mmol) was added drop by drop while the mixture was being stirred. As the reaction was exothermic, the ether refluxed. After stirring for 30 min 8.01 g (30 mmol) of α-bromocyclohexyl phenyl ketone[6] (1) dissolved in 50 ml of dry ether was added dropwise with continued stirring. This reaction was also exothermic and the ether again was refluxed. Five minutes after the addition of the bromo ketone, a thin layer chromatography (silica gel H on 5 × 15 cm plate, 50:50 hexane–benzene system) showed that the bromo ketone had disappeared completely. The mixture was poured into a separatory funnel containing a mixture of 200 g of ice, 200 ml of water, and 200 ml of pentane. After shaking the mixture thoroughly, the pentane layer was quickly separated and dried over K_2CO_3 for 10 min. The solution was filtered and the solvent was evaporated off under reduced pressure at room temperature. The residue was evaporatively distilled (bath temperature 90–100°, 0.01 mm) to give 5.2 g (75%) of **3** as a colorless liquid. An analytical sample was made by redistilling the compound evaporatively, $n^{25}D$ 1.5870.

(15) The stability of the natural product cyclopenin [H. Smith, P. Wegfahrt, and H. Rapoport, *J. Amer. Chem. Soc.*, **90**, 1668 (1968)] and that of a recently reported epoxyamine with a quinuclidinone system [D. L. Coffen and D. G. Korzan, *J. Org. Chem.*, **36**, 390 (1971)] lends further support for this view.

(16) C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

(17) D. Ginsberg and R. Pappo, *J. Amer. Chem. Soc.*, **75**, 1098 (1953).

(18) For Beckmann rearrangements using polyphosphoric acid as catalyst, see E. C. Horning and V. L. Stromberg, *ibid.*, **74**, 2680 (1952).

(19) M. Ohno, N. Narause, S. Torimitsu, and I. Teresara [*ibid.*, **88**, 3168 (1966)] report the synthesis of ω-cyanoaldehydes by second-order Beckmann rearrangement of 2-alkoxy-, 2-ethylthio-, and 2-alkylaminocycloalkanone oximes with phosphorus pentachloride.

(20) C. Hauser, F. Swamer and B. Ringler, *ibid.*, **70**, 4023 (1948).

(21) All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer (Model 237B) grating spectrophotometer. Nuclear magnetic resonance spectra were run in $CDCl_3$ using a Varian Associates A-60 spectrometer with tetramethylsilane as internal standard. The pK_a's were determined in 50% aqueous methanol. Elemental analyses were provided by Midwest Microlab, Inc., Indianapolis, Ind.

(22) Dow Chemical Co., Midland, Mich., is gratefully acknowledged for a generous gift of ethylenimine.

(23) Available from Foote Mineral Co., Exton, Pa.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.65; H, 8.51; N, 6.12.

In subsequent preparations of **3**, the yield ranged from 65 to 78%. An attempted fractionation of the liquid at 0.001 mm resulted in excessive polymerization, only part of it distilling over at 90–95°. The compound was crystallized by cooling a pentane solution in a Dry Ice–acetone bath, mp 20–22°.

Compound **3** (545 mg) was treated with 10 ml of 0.5 *N* HCl at room temperature. Hydrolysis took place almost instantaneously. The product was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 440 mg (90%) of **6**, mp 49–50°, undepressed on mixing with an authentic sample of **6**.

1-(α-1-Aziridinylbenzyl)cyclohexanol (5).—A solution of 500 mg of $NaBH_4$ in 20 ml of CH_3OH at 0° was added to 2.29 g (10 mmol) of **3** and the mixture was stirred magnetically. An additional 1.0 g of $NaBH_4$ was added in small portions to this solution. Stirring was continued at room temperature for 12 hr. Most of the CH_3OH was evaporated under reduced pressure. The product crystallized out on adding water to the mixture. It was filtered, washed with water, and dried to give 1.75 g (75%) of **5**, mp 110–112°. A small sample was recrystallized from hexane for analysis: mp 113–114°; nmr τ 2.7 (s, 5, aromatic), 7.12 (s, 1, benzilic), 7.68 (s, 1, OH), and 7.8–9.2 (complex m, 14).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.70; H, 9.25; N, 6.11.

α-Hydroxycyclohexyl Phenyl Ketone *N*-Ethylimine (9).—A mixture of 4.08 g (20 mmol) of **6**, 20 ml of ethylamine, and 5.0 g of K_2CO_3 (anhydrous) was heated in a sealed tube at 100° for 6 days. The mixture was extracted with ether and the solvent was evaporated to dryness. The residue was distilled evaporatively [bath temperature 100–105° (0.01 mm)] to give 3.9 g (85%) of **9** which crystallized on storage in the refrigerator, mp 36–38°. It was recrystallized from hexane for analysis, mp 38–39°, ir (neat) 1650 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.61; H, 9.29; N, 6.18.

1-(α-*N*-Ethylaminobenzyl)cyclohexanol (10). A. By the Hydrogenation of 3.—A solution of 1.7 g (7.4 mmol) of **3** in 50 ml of CH_3OH was hydrogenated at atmospheric pressure in the presence of 250 mg of 10% Pd/C. Over a period of 3 hr, 310 ml (94%) of H_2 was absorbed. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether and converted to the HCl salt by adding a solution of HCl in isopropyl alcohol. The crystalline material was filtered and recrystallized twice from ethanol–ether to give 1.6 g (80%) of **10** as the HCl salt, mp 223–224° dec.

Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.75; H, 8.96; N, 5.19. Found: C, 66.63; H, 8.91; N, 5.05.

B. By the Hydrogenation of 5.—A solution of 231 mg (1 mmol) of **5** in 10 ml of ethanol was hydrogenated and worked up as in the previous experiment to give 233 mg (85%) of **10** as HCl salt, mp 222–224° dec.

C. By the Reduction of 9.—A solution of 462 mg (2 mmol) of **9** in CH_3OH was reduced with 250 mg of $NaBH_4$ under the standard conditions. After 6 hr, CH_3OH was evaporated and water was added to the residue. The mixture was extracted with ether and dried (K_2CO_3) and HCl in isopropyl alcohol was added to the filtrate. The crystalline material was filtered and recrystallized from ethanol–ether to give 455 mg (85%) of **10** as the HCl salt, mp 222–224° dec. Samples of **10** prepared by methods A, B, and C were shown to be identical by mixture melting point determinations.

1-(α-1-Aziridinyl-α-methoxybenzyl)cyclohexanol (7).—Epoxyamine **3** (532 mg, 2.41 mmol) was dissolved in 10 ml of absolute CH_3OH and a drop of a saturated solution of HCl in isopropyl alcohol was added. The mixture was kept at room temperature for 3 hr and the solvent was removed *in vacuo*. The residue was recrystallized from hexane to give 470 mg (70%) of **7**: mp 124–125°; ir ($CHCl_3$) 3560 cm^{-1} (OH) and no C=O; nmr ($CDCl_3$) τ 6.8 (s, 3, OCH_3), 7.5 (s, 1, OH), 7.95 and 8.25 (q's, 2 each, aziridinyl group).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.53; H, 8.99; N, 5.52.

Compound **7** (100 mg) was hydrolyzed with 2 *N* HCl at room temperature for 2 hr. The product was extracted with ether and dried (K_2CO_3) and the solvent was removed. The residue on recrystallization from hexane gave 45 mg (58%) of α-hydroxycyclohexyl phenyl ketone (**6**), mp 49–50°.

A solution of 500 mg (1.91 mmol) of **7** in ethyl acetate was hydrogenated at atmospheric pressure in the presence of 150 mg of 10% Pd/C. The product, isolated as the HCl salt, gave 428 mg (83%) of **10**, mp 222–223° dec.

α-Hydroxycyclohexyl Phenyl Ketone *N*-(2-Benzoyloxyethyl)-imine (11). A. From Epoxyamine 3.—A solution of a mixture of 1.43 g (6.24 mmol) of **3** and 761 mg (6.24 mmol) of benzoic acid in 50 ml of dry hexane was refluxed on a steam bath for 3 hr. The solvent was evaporated and the residue was crystallized from hexane to give 1.55 g (71%) of **11**, mp 80–83°. Recrystallization from hexane gave raised mp 86–87°; ir ($CHCl_3$) 3300 cm^{-1} (OH), 1720 (ester C=O), 1650 (C=N); nmr ($CDCl_3$) τ 5.5 (t, 2, $-OCH_2$), 6.6 (t, 2, $=NCH_2$).

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.40; H, 7.06; N, 4.08.

B. From Compound 7.—A mixture of 261 mg (1.0 mmol) of **7** and 122 mg (1.0 mmol) of benzoic acid was dissolved in 10 ml of dry benzene and refluxed on a steam bath for 4 hr. The solvent was removed and the residue was recrystallized from hexane to give 210 mg (60%) of **11**, mp 84–85°.

Imino ester **11** (100 mg) was hydrolyzed with 10 ml of 2 *N* HCl at room temperature for 2 days to give 28 mg (48%) of **6**, mp 49–50°.

1-(α-2-Hydroxyethylaminobenzyl)cyclohexanol (12). A. By the Hydrolysis of 5.—Compound **5** (200 mg) was heated with 10 ml of 1 *N* perchloric acid on a steam bath for 12 hr. The mixture was extracted with ether to remove any neutral by-products. The aqueous layer was basified with NaOH and extracted repeatedly with ether. The ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was recrystallized from hexane to give 81 mg (39%) of **12**, mp 77–78°.

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.47; H, 9.48; N, 5.73.

B. From the $NaBH_4$ Reduction of 11.—Sodium borohydride (600 mg) was added in small portions to a solution of 300 mg of **11** in CH_3OH while the mixture was stirred magnetically. The stirring was continued for 7 hr at room temperature. Most of the methanol was evaporated under reduced pressure and water was added to the residue. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 135 mg (64%) of **12**, mp 77–78°.

1-(α-2-Benzoyloxyethylaminobenzyl)cyclohexanol (13). A. By the Hydrogenation of 11.—A solution of 351 mg (1.0 mmol) of **11** in 20 ml of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 100 mg of 10% Pd/C for 6 hr. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was crystallized from hexane to give 248 mg (70%) of **13**: mp 103–104°; ir ($CHCl_3$) 1705 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 5.65 (t, 2, OCH_2) and 7.2 (t, 2, $-NCH_2$).

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.65; H, 7.69; N, 3.89.

B. From 5.—A mixture of 231 mg (1.0 mmol) of **5** and 122 mg (1.0 mmol) of benzoic acid was dissolved in 20 ml of dry benzene and refluxed on a steam bath for 1 hr. The solvent was evaporated and the residue was recrystallized from hexane to give 245 mg (83.5%) of **13**, mp 103–104°.

A solution of 100 mg of **13** in 5 ml of CH_3OH was hydrolyzed by treating with 100 mg of NaOH in 3 ml of water at room temperature for 1 hr. The mixture was diluted with water and most of the methanol was evaporated under reduced pressure. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 62 mg (88%) of **12**, mp 76–77°.

1-(α-1-Aziridinyl-α-methylbenzyl)cyclohexanol (15a).—A 1.7 *M* methyllithium[23] solution in ether (10 ml, 17 mmol) was added dropwise with stirring to a solution of 1.42 g (6.1 mmol) of **3** in 20 ml of ether under a nitrogen atmosphere. After stirring at room temperature for 5 hr, the mixture was poured into water and extracted with ether. The ether solution was dried (K_2CO_3) and evaporated to dryness. The residue was crystallized from hexane to give 750 mg of **15a**, mp 108–109°.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.30; H, 9.44; N, 5.71. Found: C, 78.60; H, 9.54; N, 6.01.

A part of **15a** was converted to the perchlorate salt by treating it with an ether solution of anhydrous perchloric acid. The salt was recrystallized from acetone–ether, mp 163–164°.

Anal. Calcd for $C_{16}H_{24}ClNO_5$: C, 55.58; H, 7.00; N, 4.05. Found: C, 55.60; H, 6.95; N, 3.96.

1-(α-Methyl-α-2-hydroxyethylaminobenzyl)cyclohexanol (16a).—A mixture of 500 mg (2.2 mmol) of **15a** and 25 ml of 1 *N* perchloric acid was heated on a steam bath for 12 hr. The neutral by-products from the reaction mixture were removed by extraction with ether and the aqueous solution was basified with NaOH. The mixture was repeatedly extracted with ether, and the ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was crystallized from hexane to give 375 mg (70%) of **16a**, mp 131–132°.

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.95; H, 9.56; N, 5.32. Found: C, 72.72; H, 9.44; N, 5.27.

1-(α-1-Aziridinyl-α-phenylbenzyl)cyclohexanol (15b).—A 2 *M* solution of phenyllithium[24] in ether–benzene (40 ml, 80 mmol) was added dropwise with stirring to a solution of 5.8 g (25.3 mmol) of **3** in 50 ml of ether under a nitrogen atmosphere. After stirring at room temperature for 12 hr, the mixture was poured into water and extracted repeatedly with ether. The ether extracts were dried (K_2CO_3) and evaporated to dryness. The residue was recrystallized from acetone to give 6.2 g (81%) of **15b**, mp 154–155°.

Anal. Calcd for $C_{21}H_{25}NO$: C, 82.03; H, 8.20; N, 4.56. Found: C, 81.73; H, 8.07; N, 4.50.

A part of **15b** was converted to the perchlorate salt, mp 174–177°.

Anal. Calcd for $C_{21}H_{26}ClNO_5$: C, 61.81; H, 6.42; N, 3.43. Found: C, 61.82; H, 6.46; N, 3.27.

Another portion of **15b** was dissolved in ethyl acetate and treated with an excess of HCl in ethyl acetate to give 1-(α-phenyl-α-chloroethylaminobenzyl)cyclohexanol hydrochloride (**14b**), mp 211–212° after recrystallization from ethanol–ether.

Anal. Calcd for $C_{21}H_{27}Cl_2NO$: C, 66.28; H, 7.15; N, 3.68. Found: C, 65.89; H, 7.25; N, 3.67.

1-(α-Phenyl-α-2-hydroxyethylaminobenzyl)cyclohexanol (16b).—Compound **15b** (500 mg) was converted to 85 mg of **16b**, mp 132–133°, under the same conditions for the preparation of **14b**.

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.47; H, 8.33; N, 4.30. Found: C, 77.18; H, 8.39; N, 4.63.

2-(1-Aziridinyl)-2-phenylcycloheptanone (17). A. By the Rearrangement of 3.—A solution of 5.53 g (23.3 mmol) of **3** in 30 ml of *o*-dichlorobenzene was refluxed under a nitrogen atmosphere on a metal bath at 190–195° for 15 hr. The reaction mixture was cooled and the solvent was removed under vacuum (0.01 mm) at 40–50°. The residue was evaporatively distilled (bath temperature 90–100°, 0.01 mm) to give 2.06 g (38.65%) of **17**, ir (neat) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.75; H, 8.32; N, 5.95.

In subsequent experiments the yield of **17** ranged from 30–40%.

B. By the Rearrangement of 7.—A solution of 1.0 g of **7** in 10 ml of *o*-dichlorobenzene was refluxed under a nitrogen atmosphere on a metal bath at 190–195° for 24 hr. The reaction mixture was cooled and worked up as in A above to give 456 mg (40%) of **17**, ir superimposable with that of the product from A.

A portion of **35** was dissolved in ether and was treated with an excess of HCl in ethyl acetate. The crystalline material was filtered and recrystallized from ethanol–ether to give 2-(2-chloroethyl)amino-2-phenylcycloheptanone hydrochloride (**21**), mp 205–207° dec, ir (KBr) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{21}Cl_2NO$: C, 59.63; H, 7.00; Cl, 23.46; N, 4.63. Found: C, 59.69; H, 6.88; Cl, 23.59; N, 4.89.

2-(1-Aziridinyl)-2-phenylcycloheptanol (18).—A solution of 458 mg (2 mmol) of **17** in 20 ml of ethanol was cooled in an ice bath and stirred magnetically. $NaBH_4$ (300 mg) was added in small portions. The mixture was stirred at room temperature for 12 hr. Most of the ethanol was removed and water was added to the residue. The mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was crystallized from hexane to give 328 mg (71%) of **18**, mp 124°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.82; H, 9.15; N, 6.22.

The crystalline material, as indicated by the sharp melting point, consisted of only one, presumably the trans isomer.[25]

2-*N*-Ethylamino-2-phenylcycloheptanone (20).—A solution of 635 mg (2.73 mmol) of **17** in 20 ml of dry ethyl acetate was hydrogenated at atmospheric pressure in the presence of 100 mg of 10% Pd/C. One mole of H_2 was absorbed over a 2-hr period. The catalyst was filtered and the filtrate was evaporated to dryness. The residue was redissolved in ether and a solution of HCl in ethyl acetate was added until precipitation was complete. It was filtered and recrystallized from ethanol–ether to give 650 mg (88%) of **20** as the HCl salt, mp 226–228° dec. One more crystallization from the same solvent gave raised mp 233–235° dec, ir (KBr) 1705 cm^{-1} (C=O), $pK_a' = 7.70$.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.30; H, 8.28; N, 5.23. Found: C, 67.59; H, 8.34; N, 5.41.

2-*N*-Ethylamino-2-phenylcycloheptanone Oxime (23). A. From Amino Ketone 20.—A mixture of 200 mg of amino ketone (**20**) hydrochloride, 400 mg of hydroxylamine hydrochloride, 5 ml of pyridine, and 5 ml of ethanol was refluxed on a steam bath for 6 hr. All the volatile materials were removed under reduced pressure and water was added to the residue. The solution was neutralized with NaOH and the mixture was extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 135 mg (64%) of **23**, mp 105–106°, $pK_a' = 8.75$.

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.94; H, 8.91; N, 11.27.

B. From 2-Chloro-2-phenylcycloheptanone Oxime[17] (22).—A mixture of 4.3 g of **22**, 6 ml of ethylamine, and 200 ml of benzene was stirred in a stoppered flask at room temperature for 110 hr. The benzene solution was concentrated to 50 ml and extracted with 2 *N* HCl. The acid solution was basified with NaOH, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The residue was recrystallized from hexane to give 125 mg (3%) of oxime **23**, identical in all respects with the product from A above.

6-Benzoylhexanamide (26).—A mixture of 200 mg of **23** and 12.0 g of polyphosphoric acid[26] was heated on a steam bath with occasional shaking for 3 hr, by which time the oxime had completely disappeared. The mixture was cooled and poured onto ice. It was diluted with 100 ml of water and neutralized with NaOH. The white precipitate formed was extracted with ether and dried (K_2CO_3), and the solvent was removed. The residue was recrystallized from $CHCl_3$–ether to give 125 mg (60%) of **26**, mp 107–108°, ir ($CHCl_3$) 1675 (C=O), 3530, and 3410 cm^{-1} ($-NH_2$).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.14; H, 7.92; N, 6.41.

Amide **26** (51 mg) was hydrolyzed with NaOH in aqueous alcohol to give 46 mg (90%) of 6-benzoylhexanoic acid (**25**), mp 82–83°. The melting point of a mixture of this acid with an authentic sample of **25** was undepressed.

α-(1-Aziridinyl)cyclohexyl Phenyl Ketone (19).—A mixture of 5.3 g of 2-methoxy-2-phenyl-1-oxaspiro[2.5]octane[6] and 10.1 g of ethylenimine was heated in a sealed tube at 125–130° for 36 hr. The volatile materials were removed and the residue (6.57 g) was fractionated at 0.01 mm. The fraction boiling at 102–105° was collected and redistilled evaporatively to give 4.13 g (66.4%) of **19**, n^{25}D 1.5502, ir (neat) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.52; H, 8.49.

A solution of HCl in ethyl acetate was added with shaking to a portion of **19** dissolved in ether. The product was recrystallized from ethanol–ether to give α-(2-chloroethyl)aminocyclohexyl phenyl ketone hydrochloride (**28**), mp 183–185° dec.

Anal. Calcd for $C_{15}H_{21}Cl_2NO$: C, 59.63; H, 7.00; Cl, 23.46; N, 4.63. Found: C, 59.71; H, 6.89; Cl, 23.26; N, 4.82.

Attempted Rearrangement of 19.—A solution of 830 mg of **19** in 16 ml of *o*-dichlorobenzene was refluxed on a metal bath at 190–195° for 18 hr under a nitrogen atmosphere. An ir spectrum of the cooled mixture showed only one C=O band, at 1675 cm^{-1}. The solvent was removed at 50–60° under 0.01 mm and the residue was evaporatively distilled (bath temperature 90°, 0.01 mm) to give 450 mg (55%) of **19**. The ir spectrum of this product was superimposable with that of the starting material.

1-(1-Aziridinyl)-1-α-hydroxybenzylcyclohexane (29).—A solution of 1.1 g (4.8 mmol) of **29** in methanol was reduced with 1.0 g of $NaBH_4$ at room temperature for 12 hr. The product,

(24) Purchased from Alpha Inorganics, Inc., Beverly, Mass.

(25) Sodium borohydride reduction of α-amino ketones in six-membered ring system has been shown to give predominantly the trans isomer. *Cf.* C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. D. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).

(26) Purchased from Matheson Coleman and Bell, Norwood (Cincinnati), Ohio, and the sample contained 82.84% of phosphorus pentoxide.

after the usual work-up, was recrystallized from hexane to give 1.0 g (90%) of **29**, mp 90–91°.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.80; H, 9.18.

A part of **29** was converted to the perchlorate salt, mp 159–160° after recrystallization from acetone–ether.

Anal. Calcd for $C_{15}H_{22}ClNO_5$: C, 54.33; H, 6.68; N, 4.22. Found: C, 54.12; H, 6.66; N, 4.18.

Another part of **29** was dissolved in ether and treated with an excess of HCl in ethyl acetate to give 1-(2-chloroethyl)amino-1-α-hydroxybenzylcyclohexane hydrochloride (**30**), mp 216° dec, after recrystallization from ethanol–ether.

Anal. Calcd for $C_{15}H_{23}Cl_2NO$: C, 59.23; H, 7.62; N, 4.60. Found: C, 59.02; H, 7.59; N, 4.54.

Registry No.—**3**, 15817-11-5; **5**, 15817-31-9; **7**, 32515-75-6; **9**, 32515-76-7; **10** HCl, 15946-21-1; **11**, 32515-78-9; **12**, 32515-79-0; **13**, 32515-80-3; **14b**, 32515-81-4; **15a**, 32515-82-5; **15a** perchlorate, 32515-83-6; **15b**, 32515-84-7; **15b** perchlorate, 32515-85-8; **16a**, 32515-86-9; **16b**, 32515-87-0; **17**, 15817-32-0; **18**, 32515-89-2; **19**, 32515-90-5; **20** HCl, 15817-12-6; **21**, 32515-98-3; **23**, 15885-97-9; **26**, 15817-09-1; **28**, 32515-94-9; **29**, 32515-95-0; **29** perchlorate, 32515-96-1; **30**, 32515-97-2.

Acknowledgment.—The authors thank Dr. K. Grant Taylor for useful discussions. Financial support from the National Science Foundation, Grant GP 8272, is gratefully acknowledged.

A New Type of Basic Amide Hydrolysis, Characterized by Alkyl–Nitrogen Fission

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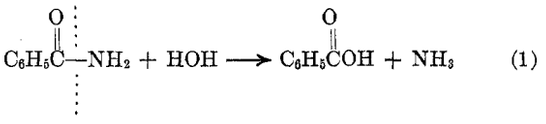
Received July 2, 1971

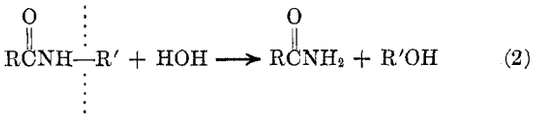
Amides of the type $RNHCH(R')C_6H_4N{=}NR^2$ [R = alkyl C=O, aryl C=O, alkyl SO_2, aryl SO_2, $H_2NC{=}O$, $C_6H_5NHC{=}O$, $(C_6H_5)_2NC{=}O$; R^1 = H, CH_3, C_6H_5; R^2 = phenyl, substituted phenyl, naphthyl] undergo basic hydrolysis under mild conditions to give RNH_2 and $R^1C(=O)C_6H_4NHNHR^2$. A similar reaction occurs when the substituents are ortho to one another. No reaction takes place when the groups are in the meta position. The effects of structural modifications on the course of the reaction were studied, and a mechanism for the reaction has been proposed.

In 1832, Liebig and Wöhler[2] described the first hydrolysis of an acyl amide in their classical paper on the benzoyl radical; the base-catalyzed reaction proceeded *via* the now familiar acyl–nitrogen cleavage (eq 1). It



(1)

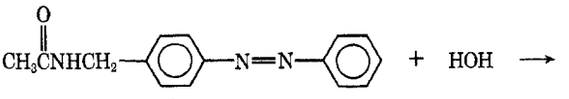
was not until 1960 that a second type of amide hydrolysis became known. In that year, Lacey[3] reported that under acid conditions some highly branched amides hydrolyze with alkyl–nitrogen fission (eq 2).



(2)

Work here has now shown that this second type of cleavage also occurs in basic solution with certain amides containing an azo group.

The "amidazo" reaction was encountered during an attempt to prepare *p*-phenylazobenzylamine by saponification of its acetyl derivative **1**; instead of the anticipated behavior, a more complicated reaction was observed (eq 3). Reaction conditions consisted of 3-hr refluxing under nitrogen in 0.36 *N* KOH in alcohol, 1.2 mol of alkali being used per mol of amide; the yields of acetamide and 4-formylhydrazobenzene (**2**) were 37 and 62%, respectively.



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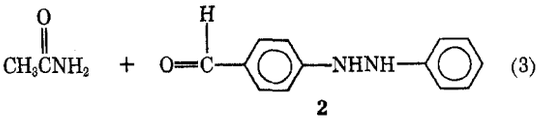
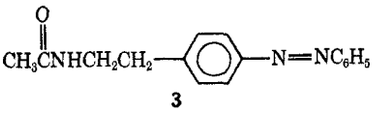


2 (3)

This novel reaction appeared to be of sufficient theoretical interest to warrant further scrutiny; so a study of its general nature was undertaken. First, some limitations of the reaction were established by demonstrating that the following compounds do not undergo alkyl–nitrogen cleavage when refluxed with alcoholic KOH.



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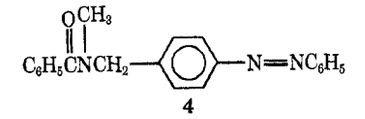

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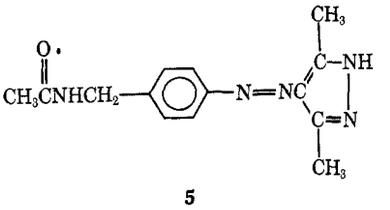

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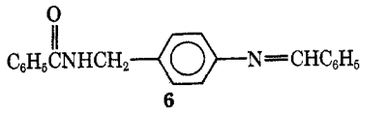

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(1) This is a laboratory of the Northern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) J. von Liebig and F. Wöhler, *Justus Liebigs Ann. Chem.*, **3**, 268 (1832).

(3) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960).