The Neber Rearrangement of Substituted Desoxybenzoin Oxime Toxylates

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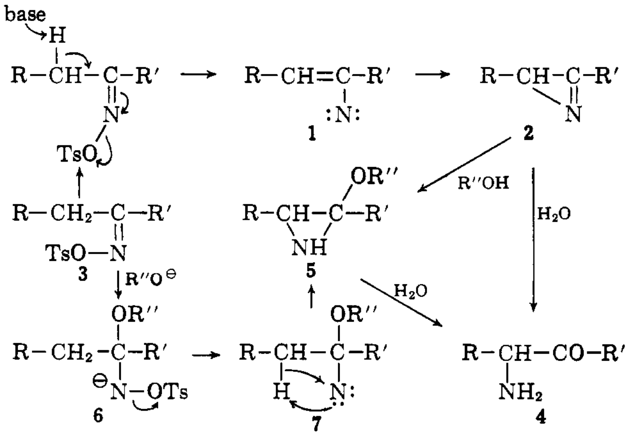
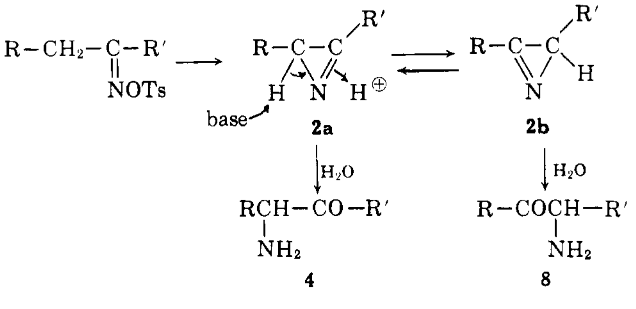
Application of the Neber reaction to the oxime tosylates (*anti*-benzyl or *p*-methylbenzyl) of desoxybenzoin and 4-methyl- and 4′-methyldesoxybenzoin produced the α-acetamido derivative of the corresponding ketone in each case. From the reaction of these derivatives of desoxybenzoin, one of the neutral by-products was the tosyl ester of corresponding benzoin.

The Neber rearrangement,[1] as well as the rearrangement of N,N-dichloroamines,[2] has been suggested[1] to involve an unsaturated nitrene[3] intermediate **1** which closes to an azirine **2**[4] in a manner analogous to the closure of a vinylcarbene to a cyclopropene.[5] Although azirines **2** have been isolated[1a] from oxime tosylates **3** with activated methylene groups, the usual product isolated is the hydrolysis product **4** or an alkoxyethylenimine **5**.[1b] In cases where the oxime tosylate **3** does not have an especially active adjacent methylene group, the possibility that the reaction proceeds by initial addition of alkoxide ion (to form **6**) followed by formation of the nitrene **7** and insertion into an adjacent C—H bond has not been excluded.[6]



In the course of investigating the chemistry of oxime and hydroxylamine derivatives, the question arose whether the Neber rearrangement might lead to isomeric amino ketones **4** and **8** by the indicated isomerization (**2a** ⇌ **2b**)[7] of an azirine intermediate. Although previous studies[1] offered no support for this possibility, it was desirable to examine this question critically in a case where the two tautomeric azirines would be essentially equivalent electronically. Accordingly, the experiments summarized in Chart 1 were performed. The results indicated clearly that a symmetrical intermediate or a rapidly equilibrating mixture of intermediates (*e.g.*, **2a** ⇌ **2b**) is not involved in the Neber rearrangement. From experiments currently in progress we hope to distinguish between the possibilities that the tosyloxy group is eliminated directly from the oxime derivative to form **1** or that the elimination is preceded by addition of alkoxide to form **6**.



From the reactions of the oxime tosylates **3**, the neutral fraction contained, in addition to the ester **14** that was derived from solvolysis of the oxime tosylate, the tosyl ester **15** of the corresponding benzoin. The location of the tosylate group in the unsymmetrical benzoins **15b** and **15c** was demonstrated by reductive cleavage[8] to the starting ketone **9**. In one case (**3c**), treatment of the insoluble portion of the reaction mixture with acetic acid produced the analogous acetate **18c**. Although several pathways such as **3** → **22** → **21** → **15** (during the reaction) or **19** → **2** → **20** → **21** → **15** (during the isolation; this same sequence could explain the formation of **18c**)[8b,8c] can be envisioned for the formation of the keto tosylates **15**, our efforts to obtain experimental evidence bearing on this point have thus far been unsuccessful. The small amounts of acetamido ketone **16a** formed when the insoluble portion of the reaction mixture from **3a** was treated with acetic acid may represent an alternative mode of reaction of **19a** with acetic acid which is mechanistically analogous to the reaction of 1-alkoxy-1,2-epoxides with carboxylic acids.[8b]

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(1) For discussion and leading references see (a) D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, **75**, 33 (1953); (b) M. J. Hatch and D. J. Cram, *ibid.*, **75**, 38 (1953).

(2) H. E. Baumgarten and J. M. Petersen, *ibid.*, **82**, 459 (1950).

(3) The neutral, electron-deficient nitrogen species, $R-\ddot{\underset{..}{N}}$, has been called a nitrene, (a) D. H. R. Barton and L. R. Morgan, *Proc. Chem. Soc.*, 206 (1961); (b) R. A. Abramovitch, Y. Ahmad, and D. Newman, *Tetrahedron Letters*, No. **21**, 752 (1961); an imine, (c) W. Kirmse, *Angew. Chem.*, **71**, 537 (1959); and an azene, (d) P. A. S. Smith and J. H. Hall, *J. Am. Chem. Soc.*, **84**, 480 (1962).

(4) (a) G. Smolinsky [*J. Am. Chem. Soc.*, **83**, 4483 (1961); *J. Org. Chem.*, **27**, 3557 (1962)] has recently demonstrated the practicality of this ring closure by the isolation of an azirine from the pyrolysis of a vinyl azide; other examples of the formation of aziridines include (b) W. Lwowski and T. W. Mattingly, *Tetrahedron Letters*, No. **7**, 277 (1962); (c) E. Schmitz, *Chem. Ber.*, **95**, 676 (1962); (d) E. Schmitz and D. Habisch, *ibid.*, **95**, 680 (1962).

(5) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **83**, 2015 (1961).

(6) Thus far nitrenes have been reported (ref. 3a) to undergo intramolecular insertion into a C—H bond to form five-member rings. However, formation of three-membered rings (*e.g.*, **5**), from nitrenes analogous to the behavior of carbenes [L. Friedman and H. Shechter, *ibid.*, **81**, 5512 (1959)] has not been demonstrated.

(7) *Cf.* R. Perez Ossorio and E. D. Hughes, *J. Chem. Soc.*, 426 (1952).

(8) (a) F. Sondheimer, S. Kaufmann, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953). (b) In a formally but not mechanistically analogous reaction, 1-alkoxy-1,2-epoxy compounds have been found to react with carboxylic acids to form 2-acyloxy-1-keto compounds *via* intermediate 1-acyloxy-1-alkoxy-2-hydroxy intermediates; C. L. Stevens and S. J. Dykstra, *ibid.*, **75**, 5975 (1953). (c) The rearrangement depicted in structure **20** finds analogy in the isomerization of 1-acetoxy-1,2-epoxides to α-acetoxy ketones; H. J. Shine and G. E. Hunt, *ibid.*, **70**, 2434 (1958).

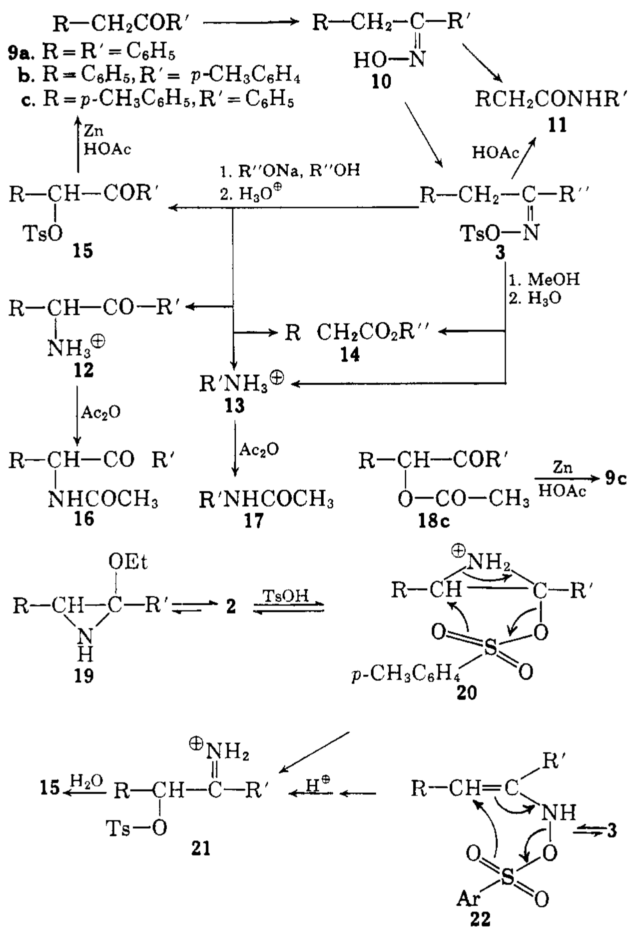

CHART I

Experimental[9]

The Tosyl Ester (3a) of *syn*-Benzyl Phenyl Ketoxime.—To a cold (−20°) solution of 31.703 g. (0.150 mole) of *syn*-benzyl phenyl ketoxime (**10a**) [m.p. 95–97° (lit.,[10] 98°)[11]], 9.92 g. (0.151 mole) of potassium hydroxide in 450 ml. of acetone, and 75 ml. of water was added, with stirring over a 23-min. period, a solution of 28.596 g. (0.150 mole) of *p*-toluenesulfonyl chloride in 150 ml. of acetone. After the mixture had been stirred for an additional 20 min. at −20°, it was poured into 300 ml. of benzene and extracted repeatedly with ice water. After the benzene solution had been dried, diluted with 600 ml. of hexane, and cooled to −25°, the tosyl ester, which separated as white needles, was collected, yield 43.29 g. (79%). The product, which melted sharply with decomposition within the range 80–90° (lit.,[1b] 81.5–83.5°) (the decomposition point was a function of the time the material was in the heating bath), was recrystallized from a benzene–hexane mixture with no apparent change in melting point behavior. The material has infrared absorption[12] at 1375, 1180, and 1193 cm.$^{-1}$ (—SO_2—O—) with no absorption in the 3-μ region attributable to an N—H or O—H function.

Anal. Calcd. for $C_{21}H_{19}NSO_3$: C, 69.02; H, 5.24; N, 3.83; S, 8.77. Found: C, 69.02; H, 5.13; N, 3.84; S, 8.71.

A solution of 329 mg. (0.90 mmole) of the tosyl ester **3a** in 90 ml. of acetic acid was allowed to stand at room temperature for 12 hr.[13] and then was concentrated under reduced pressure. A solution of the residue in chloroform was washed with aqueous sodium bicarbonate, dried, and concentrated. Recrystallization of the residual solid afforded 116.9 mg. (61.6%) of phenylacetanilide (**11a**), m.p. 115–116.5°, identified with an authentic sample by a mixed melting point determination and comparison of infrared spectra.

A solution of 5.00 g. (0.0137 mole) of the tosyl ester in a mixture of 50 ml. of benzene, 100 ml. of methanol, and 1 ml. of water was allowed to stand at room temperature for 44 hr. and then was concentrated under reduced pressure. The residue (6.118 g.) was washed with benzene and with ether to leave 3.18 g. (87.7%) of the aniline salt (**13a**) of *p*-toluenesulfonic acid, m.p. 238–240° dec. (lit.,[14] 238°), identified with an authentic sample by comparison of infrared spectra and a mixed melting point determination. After the combined benzene and ether extracts had been washed successively with dilute aqueous hydrochloric acid and aqueous sodium bicarbonate, dried, and concentrated, a solution of the residue in hexane deposited 153 mg. (5%) of phenylacetanilide (**11a**), m.p. 115–117°. After concentration of the remaining hexane solution, distillation in a short path still (100–135° at 0.1 mm.) separated 1.293 g. (62.8%) of methyl phenylacetate (**14a**, $R'' = CH_3$) identified with an authentic sample by its retention time on gas chromatography and by comparison of infrared spectra.

The Tosyl Ester (3b) of *syn*-Benzyl *p*-Tolyl Ketoxime.—Benzyl *p*-tolyl ketone (**9b**), white prisms from acetone melting at 107.4–108.4° (lit.,[15] 107.5°) semicarbazone as white needles from aqueous ethanol melting at 163.8–165.3° (lit.,[16] 166–167°), was prepared in 63% yield by the acylation of toluene with phenacetyl chloride.[17] A 2.1-g. (0.01 mole) sample of the ketone was converted to *syn*-benzyl *p*-tolyl ketoxime (**10b**) as white crystals from ethanol, m.p. 128.5–129.8° (lit.,[18] 130–131°), yield 1.73 g. (77%), by the procedure of Jenkins.[10] To establish the configuration, a 1.126-g. (5.0 mmoles) sample of the oxime in ether was treated with phosphorus pentachloride[11b] as previously described.[10] The rearranged product, N-(*p*-tolyl)phenylacetamide (**11b**), was separated from a hexane–ethyl acetate mixture as white plates, m.p. 129.7–131.7°, yield 882 mg. (78%). This product, whose melting point was raised to 132–133.8° (lit., 135–136°,[19a] 132–133°[19b])[20] was identified with an authentic sample[21] by a mixed melting point determination and comparison of infrared spectra.

The reaction of 9.011 g. (0.04 mole) of the oxime **10b**, 2.77 g. (0.042 mole) of potassium hydroxide and 7.626 g. (0.04 mole) of *p*-toluenesulfonyl chloride in aqueous acetone was carried out as previously described. After the resulting benzene solution had been dried, diluted with hexane, and cooled, 11.31 g. (74%) of the white, crystalline tosyl ester **3b**, m.p. 63° dec. (dependent on time of heating), was separated. The product, which was recrystallized from a benzene–hexane mixture at −20° without further change in its properties, has infrared absorption[12] at 1380, 1194, and 1180 cm.$^{-1}$ (—SO_2O) with no absorption in the 3-μ region attributable to an N—H or O—H function.

Anal. Calcd. for $C_{22}H_{21}NSO_3$: C, 69.63; H, 5.58; N, 3.69; S, 8.45. Found: C, 69.59; H, 5.63; N, 3.41; S, 8.47.

A solution of 5.692 g. (0.015 mole) of the oxime tosylate **3b** in 400 ml. of acetic acid was allowed to stand at room temperature for 11 hr. and then worked up as previously described to separate 3.032 g. (89.6%) of N-(*p*-tolyl)phenylacetamide, m.p. 131.3–133.3°, identified with an authentic sample[21] by a mixed melting point determination and comparison of infrared spectra.

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[9] All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer.

[10] S. S. Jenkins, *J. Am. Chem. Soc.*, **55**, 703 (1933).

[11] (a) The configuration of this oxime has been established by its rearrangement (ref. 10) to phenylacetanilide (**11a**) in the presence of phosphorus pentachloride and ether. (b) These conditions for Beckmann rearrangement have been found [L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960)] most reliable for determining the configuration of oximes.

[12] Determined in chloroform solution.

[13] The procedure of W. Z. Heldt, *J. Am. Chem. Soc.*, **80**, 5880 (1950).

[14] O. C. Dermer and V. H. Dermer, *J. Org. Chem.*, **7**, 581 (1942).

[15] W. Mann, *Ber.*, **14**, 1645 (1881).

[16] R. R. Otter and R. L. Shriner, *J. Am. Chem. Soc.*, **73**, 887 (1951).

[17] The procedure of C. F. H. Allen and W. E. Barker ("Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 156) was employed.

[18] M. A. Mailhe, *Bull. soc. chim. France*, **15**, 324 (1914).

[19] (a) A. Purgathi, *Gazz. chim. ital.*, **20**, 172 (1890); (b) C. A. Bischoff and P. Walden, *Ann.*, **279**, 118 (1894).

[20] See also I. Boeseken, *Rec. trav. chim.*, **16**, 297 (1897).

[21] An authentic sample of N-(*p*-tolyl)phenylacetamide, m.p. 131.5–133.2°, was obtained in 51% yield from reaction of *p*-toluidine with phenacetyl chloride in pyridine. The alternative Beckmann rearrangement product, N-benzyl-*p*-toluamide melting at 133.2–134.5° (lit.,[20] 133°), was prepared by reaction of benzylamine with *p*-toluyl chloride in pyridine. These two isomeric amides have very different infrared spectra.

The Tosyl Ester (3c) of *syn*-*p*-Methylbenzyl Phenyl Ketoxime.—After a mixture of 208.6 g. (1.555 moles) of *p*-methylacetophenone, 203.3 g. (2.333 moles) of morpholine and 74.8 g. (2.333 g.-atoms) of sulfur had been refluxed for 16 hr.,[22] the hot reaction mixture was poured into 900 ml. of boiling ethanol and allowed to cool. A portion of the crude thiomorpholide (279 g. or 74.5%, m.p. 70–101°) which had been separated was recrystallized from ethanol to afford the pure **thiomorpholide of *p*-tolylacetic acid** as white needles, m.p. 102–103.3°, with no infrared absorption[23] in the 3- or 6-μ regions attributable to an N—H, O—H or C=O function and an ultraviolet[24] maximum at 281 mμ (ϵ 15,500).

Anal. Calcd. for $C_{13}H_{17}NSO$: C, 66.34; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.29; H, 7.29; N, 5.90; S, 13.49.

A solution of the remainder of the crude thiomorpholide in a mixture of 560 ml. of acetic acid, 84 ml. of concentrated sulfuric acid, and 125 ml. of water was refluxed for 5 hr.[22] and then filtered and diluted with water. The solid which separated was extracted with aqueous sodium hydroxide. Acidification of this extract followed by appropriate manipulations separated the crude ***p*-tolylacetic acid**. Recrystallization from hexane afforded 101.8 g. (44% over-all) of the pure acid as white needles, m.p. 89–90.5° (lit.,[25] 91°). Reaction of the acid with excess ethereal diazomethane followed by the usual isolation procedure afforded **methyl *p*-tolylacetate (14c**, $R'' = CH_3$) as a colorless liquid, b.p. 63.5° (0.1 mm.), n^{24}D 1.5031, with infrared absorption[23] at 1745 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.42.

Reaction of *p*-tolylacetic acid with excess thionyl chloride yielded *p*-tolylacetyl chloride, b.p. 87.5–88.3° (3 mm.), which was treated with excess aniline in benzene solution to form ***p*-tolylacetanilide (11c)**, m.p. 144–147°, yield 87%. Recrystallization from methanol afforded the pure anilide as white prisms, m.p. 147.5–149.6°, with infrared absorption[26] at 1675 cm.$^{-1}$ (amide C=O) and 1540 cm.$^{-1}$ (N—H bending) and ultraviolet absorption[24] at 243 mμ (ϵ 16,800).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.74; H, 6.45; N, 6.21.

Acylation of benzene with *p*-tolylacetyl chloride[17] produced *p*-methylbenzyl phenyl ketone **9c** as white needles from ethanol, m.p. 95–97° (lit.,[27] 94–97°), yield 73%, which formed a 2,4-dinitrophenylhydrazone, m.p. 191.8–193.8° (lit.,[28] 194–195°). The ketone **9c** was converted to *syn*-*p*-methylbenzyl phenyl ketoxime (**10c**) as white needles from hexane melting at 100–102° (lit.[28] 102–103°) by the previously described[10] procedure. Rearrangement of a 2.253-g. (0.010-mole) sample of this oxime **10c** with phosphorus pentachloride in ether[10,11b] to give 1.778 g. (79%) of *p*-tolylacetanilide (**11c**), m.p. 146–148°, identified by a mixed melting point determination, established the configuration of the oxime **10c**.

Reaction of 6.490 g. (0.0288 mole) of the oxime **10c** and 1.91 g. (0.0291) mole) of potassium hydroxide with 5.492 g. (0.0288 mole) of *p*-toluenesulfonyl chloride in aqueous acetone at −30° as previously described yielded the tosyl ester **3c** as white crystals, m.p. 64–68° dec. (dependent on time of heating), yield 6.77 g. (62%). The product had infrared adsorption[23] at 1388, 1195 and 1184 cm.$^{-1}$ ($-SO_2-O-$) with no absorption in the 3-μ region attributable to an N—H or O—H function.

Anal. Calcd. for $C_{22}H_{21}NSO_3$: C, 69.63; H, 5.58; N, 3.69; S, 8.45. Found: C, 69.73; H, 5.59; N, 3.68, S, 8.46.

A solution of 1.898 g. (0.0050 mole) of the tosyl ester **3c** in 100 ml. of acetic acid was allowed to stand at room temperature for 16 hr. and then worked up as previously described. Crystallization from an ethyl acetate–hexane mixture separated 0.936 g. (83.2%) of *p*-tolylacetanilide, m.p. 146.5–148°, identified by a mixed melting point determination.

α-Acetamidobenzyl Phenyl Ketone (**16a**).—To a mixture of 22.52 g. (0.100 mole) of benzoyl *syn*-phenyl ketoxime, m.p. 138.1–139.5° (lit.,[29] 140°), 30.63 g. (0.300 mole) of acetic anhydride and 78 g. (1.3 moles) of acetic acid was added, in portions over a 1.25-hr. period with vigorous stirring, 26.15 g. (0.400 g.-atom) of zinc dust while the temperature of the reaction mixture was maintained at 38–48°. After the addition was complete the mixture was stirred for an additional 15 min., filtered, and concentrated under reduced pressure. A solution of the residue in chloroform was washed repeatedly with water, dried, and concentrated to leave 23.71 g. of the crude acetamido ketone, m.p. 128–133°. Recrystallization from a hexane–benzene mixture afforded 19.32 g. (76.5%) of the acetamido ketone as white needles, m.p. 132–135.7°. Recrystallization gave the pure ketone, m.p. 134.6–135.7°, with infrared absorption[12] at 3460 cm.$^{-1}$ (N—H) and 1665 cm.$^{-1}$ (amide C=O) with a shoulder at 1685 cm.$^{-1}$ (conj. C=O); the product has ultraviolet maxima[24] at 248 mμ (ϵ 12,700) and 317 mμ (ϵ 267).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.10; H, 5.97; N, 5.54.

A mixture of 10.0 g. (0.0395 mole) of the acetamido ketone **16a** and 100 ml. of 20% hydrochloric acid was refluxed for 4 hr. and then concentrated to dryness under reduced pressure. After the residue had been washed with boiling benzene, it was recrystallized from ethanol to give 7.54 g. (77%) of desylamine hydrochloride as white needles melting with decomposition within the range 219–231°. Repeated recrystallization from ethanol–ether mixtures containing a small amount of concentrated hydrochloric acid afforded 3.95 g. (40.3%) of the pure amine hydrochloride, m.p. 238° dec. (dependent on time of heating, lit., 234°,[30] 243°[31]).

To a saturated, aqueous solution of 247.7 mg. (1.00 mmole) of desylamine hydrochloride was added successively 284.5 mg. (2.02 mmoles) of benzoyl chloride and a solution of 84 mg. (2.04 mmoles) of sodium hydroxide in 1 ml. of water. The mixture was heated to 40–60°, with stirring, for 0.5 hr. and then cooled and extracted with chloroform. The chloroform extract was washed successively with aqueous sodium bicarbonate and water, dried and concentrated. Recrystallization of the residue from a benzene–hexane mixture afforded 246.1 mg. (78.1%) of α-benzamidobenzyl phenyl ketone as white needles, m.p. 138.5–139.5° (lit.,[32] 139–140°).

Acetylation of a 247.8 mg. (1.00 mmole) sample of desylamine hydrochloride with acetic anhydride and sodium acetate in aqueous solution[33] afforded 200 mg. (79.1%) of the acetamido ketone **16a**, m.p. 134–135.5°. When a solution of 247 mg. (1.00 mmole) of desylamine hydrochloride and 172 mg. (1.00 mmole) of *p*-toluenesulfonic acid in 25 ml. of boiling water was allowed to cool, the *p*-toluenesulfonic acid salt of desylamine separated from the solution as white needles, m.p. 233° dec. (dependent on time of heating), yield 254 mg. (66%).

Anal. Calcd. for $C_{21}H_{21}NSO_4$: C, 65.78; H, 5.52; N, 3.65; S, 8.36. Found: C, 65.49; H, 5.44; N, 3.54; S, 8.19.

Acetylation of 383.5 mg. (1.00 mmole) of the *p*-toluenesulfonic acid salt of desylamine with excess pyridine and acetic anhydride yielded 215.6 mg. (85%) of the acetamido ketone **16a**, m.p. 133.5–136.5°.

α-Acetamidobenzyl *p*-Tolyl Ketone (**16b**).—This acetamido ketone, prepared from the ketone **9b** by bromination, reaction of the monobromo ketone, m.p. 85.4–86.4° (lit.,[34] 87–88°) with hexamethylenetetramine,[34] and subsequent acetylation with acetic anhydride in pyridine, separated from ethanol as white crystals, m.p. 112.5–115° (lit.,[34] 113.5–114.5°). The product has infrared absorption[23] at 3430 and 3330 cm.$^{-1}$ (unassoc. and assoc. N—H) and at 1674 cm.$^{-1}$ (amide C=O) with a shoulder at 1685 cm.$^{-1}$ (conj. C=O) and an ultraviolet maximum[24] at 258 mμ (ϵ 15,500).

α-Acetamido-*p*-methylbenzyl Phenyl Ketone (**16c**).—Nitrosation of the ketone **9c** with butyl nitrite and ethanolic sodium ethoxide[35] produced a mixture of the α-form, m.p. 112–114° (lit.,[36] 115°), yield 41.1%, and the β-form, m.p. 124.5–127° (lit.,[36] 134°), yield 12.7% of benzoyl *p*-tolyl ketoxime. A 2.393-g. (0.010-mole) sample of the α-form (m.p. 112–114°) of this oximino ketone was reduced and acetylated with a mixture of acetic acid, acetic anhydride, and zinc dust by the previously described procedure. The acetamido ketone **16c** crystallized from

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(22) The procedure of M. Cormack and M. A. Spielman, *Org. Reactions*, **3**, 83 (1956).

(23) Determined in carbon tetrachloride solution.

(24) Determined in ethanol solution.

(25) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907).

(26) Determined as a suspension in a potassium bromide pellet.

(27) R. L. Huang, *J. Chem. Soc.*, 4089 (1957).

(28) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **76**, 3719 (1954).

(29) T. W. J. Taylor and M. S. Marks, *J. Chem. Soc.*, 2302 (1930).

(30) P. W. Neber and G. Huh, *Ann.*, **515**, 283 (1934).

(31) R. Pschorr and F. Bruggemann, *Ber.*, **35**, 2740 (1902).

(32) A. McKenzie and F. Barrow, *J. Chem. Soc.*, **103**, 1331 (1913).

(33) The procedure of L. F. Frieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., New York, N. Y., 1955, p. 151.

(34) G. Drefahl and H. Crahmer, *Chem. Ber.*, **91**, 750 (1958).

(35) The procedure of T. W. J. Taylor, *J. Chem. Soc.*, 2018 (1931).

(36) J. Meisenheimer, *et al.*, *Ann.*, **468**, 202 (1929).

TABLE I

NEBER REARRANGEMENT OF THE OXIME TOSYLATE **3a** UNDER VARIOUS REACTION CONDITIONS

Solvent (ml.)	Base	Reaction time, hr.	Products, % yield				
			16a	**15a**	**14a**	**17a**	**11a**[a]
EtOH (30)	KOEt	15	64	0.4	6	2	2
EtOH (30)	KOEt	2	52	4	7	3	16
MeOH (30)	KOMe	2	4	0.8	1	..	81
EtOH (150)	KOEt	15	59	5	2	1	..
EtOH (30) + H_2O (0.54)	KOEt (or KOH)	2	29	3	3	2	48
EtOH (10) + PhH (20)	KOEt	15	54	..	25	23	..
EtOH (30)	NaOEt	15	63	2	4	2	2
MeOH (11) + PhH (96)	NaOMe	16	53	19	4	1	..

[a] The phenylacetanilide isolated represents both any Beckmann rearrangement which occurred during the course of the reaction and any unchanged oxime tosylate **3a** which would have been converted to this amide by the isolation precedure employed.

toluene as 1.2231 g. (46%) of white prisms of a toluene solvate (m.p. 72–80°) which melted at 74.4–74.8° after it had been dried under reduced pressure to remove the solvent. The acetamido ketone has infrared absorption[23] at 3420 and 3310 cm.$^{-1}$) (unassoc. and assoc. N—H) and at 1670 cm. (amide C=O) with a shoulder at 1685 cm.$^{-1}$ (conj. C=O) and an ultraviolet maximum[24] at 247 mμ (ϵ 11,200).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.54; H, 6.31; N, 4.94.

The Neber Rearrangement of the Oxime Tosylate 3a.—To a cold (0°) solution of potassium ethoxide, prepared from 0.67 g. (0.017 g.-atom) of potassium and 30 ml. of ethanol, was added 5.4809 g. (0.0150 mole) of the oxime tosylate **3a**. After the resulting heterogenous (the oxime tosylates **3** are only slightly soluble in ethanol) reaction mixture had been stirred for 15 hr. at 0 to −3° under a nitrogen atmosphere, the mixture was filtered and the residue (containing sodium *p*-toluenesulfonate and the unchanged oxime tosylate **3a** as well as other components) was washed with ethanol and then dissolved in 50 ml. of acetic acid. This acetic acid solution was allowed to stand overnight and then concentrated, diluted with water, and extracted with ether. After the ethereal extract had been washed with aqueous sodium bicarbonate, dried, and concentrated, crystallization of the residue from ether gave 207.4 mg. (5.5%) of α-acetamidobenzyl phenyl ketone (**16a**), m.p. 133.7–135.2°), identified by a mixed melting point determination.

Gas chromatography[37] of the mother liquor, employing the acetamido ketone **16b** as an internal standard, indicated the presence of the acetamido ketone **16a** (5% yield) and phenylacetanilide (**11a**, presumably from rearrangement of the starting material, 1% yield.) This product **11a**, isolated from a comparable experiment, melted at 117–118.3° and was identified by a mixed melting point determination and comparison of infrared spectra.

The original ethanolic solution from the reaction mixture was diluted with ether and benzene and then washed with 4 *N* aqueous hydrochloric acid. The remaining organic layer was washed with aqueous sodium bicarbonate, dried, and concentrated to leave 0.4845 g. of neutral oil from which 22 mg. (0.4%) of the tosyl ester **15a**, m.p. 107.6–109.1°, was separated by crystallization from ether and identified with the subsequently described sample by a mixed melting point determination. Gas chromatographic[38] analysis of the mother liquor, employing methyl *p*-tolylacetate as an internal standard, indicated the presence of ethyl phenylacetate (**14a**, $R'' = C_2H_5$, 6% yield). From a comparable experiment a sample of the ester **14a** was collected and identified by comparison of infrared spectra and retention times.

The aqueous acid extract of the original reaction mixture was concentrated to dryness and the residual crude amine hydrochloride was acetylated by reaction with a solution of excess acetic anhydride in pyridine for 75 min. at room temperature. After the usual isolation procedure, 1.9174 g. (50.5%) of the acetamido ketone **16a**, m.p. 134–135.5°, was isolated and identified with the previously described sample by a mixed melting point determination. Gas chromatographic analysis[37] of the mother liquor indicated the presence of the acetamido ketone **16a** (3% yield) and acetanilide (**17a**, 2% yield).

The same isolation and analytical procedure was applied to the mixtures from reactions employing other reaction conditions (Table I). From the initially homogeneous reaction of 5.4809 g. (0.0150 mole) of the oxime tosylate **3a** with sodium methoxide (0.0152 mole) in a mixture of 96 ml. of benzene and 11 ml. of methanol, the tosyl ester **15a** (1.0380 g. or 18.9%) was isolated as white prisms from an ethanol–ethyl acetate–hexane mixture, m.p. 106.7–108°. The compound has infrared absorption at 1701 cm.$^{-1}$[12] (conj. C=O) and at 1360 and 1180 cm.$^{-1}$[26] (SO_2) with ultraviolet maxima[24] at 229 mμ (ϵ 17,400) and 250 mμ (ϵ 13,600) and n.m.r. absorption[39] at 7.62 τ (3H singlet, aryl CH_3) and as 3.29 τ [1H singlet, CO(Ph)CH—SO_2—] with complex absorption in the region 2.0–3.0 τ attributable to 14 aryl protons.

Anal. Calcd. for $C_{21}H_{18}O_4S$: C, 68.83; H, 4.95; S, 8.75. Found: C, 69.06; H, 4.95; S, 8.80.

A mixture of 10.61 g. (0.050 mole) of benzoin, 9.53 g. (0.050 mole) of *p*-toluenesulfonyl chloride, 3.0 g. (0.075 mole) of powdered sodium hydroxide, and 250 ml. of benzene was stirred vigorously for 2 hr. at room temperature[40] and then poured into 200 ml. of water. After the organic layer had been dried and concentrated, a series of fractional crystallizations from a benzene–hexane mixture, from ethanol, and from carbon tetrachloride gave 1.57 g. of unchanged benzoin and 1.80 g. (11.5% based on the unrecovered benzoin) of the tosyl ester **15a**, m.p. 106–108°, identified with the previously described sample by a mixed melting point determination.

A mixture of 784.6 mg. (12 mg.-atoms) of zinc dust, 366.5 mg. (1.0 mmole) of the tosyl ester **15a**, 7.85 ml. of acetic acid, and 2.35 ml. of water was stirred at room temperature for 40 min. and then filtered and concentrated. After the concentrate had been diluted with water, it was extracted with chloroform and this extract was washed with aqueous sodium bicarbonate, dried, and concentrated. Short-path distillation (200° at 0.05 mm.) of the residual crude ketone (182 mg. or 93%, m.p. 37–45°) afforded 150.4 g. (76.7%) of desoxybenzoin (**9a**), m.p. 56–57°, identified by comparison of infrared spectra.

The Neber Rearrangement of the Oxime Tosylate 3b.—After a mixture of 5.642 g. (0.01485 mole) of the oxime tosylate **3b** and a cold (5°) solution containing 0.0161 mole of potassium ethoxide in 30 ml. of ethanol had been stirred for 4 hr., application of the previously described isolation procedure afforded 1.4595 g. (36.9%) of the keto amide **16b**, m.p. 112–115°, and 388.3 mg. (17.5%) of the amide **17b**, m.p. 144.5–147.2°. Recrystallization from an ether–benzene mixture gave 245.8 mg. of the pure amide **17b**, m.p. 149.5–150.3° (lit.,[41] 146.5–147.5°), identified by a mixed melting point determination. An ethereal solution of the neutral products deposited 415.1 mg. (7.4%) of the tosyl ester **15b** as white prisms, m.p. 124–126.5°, whose melting point was raised to 131.3–132.2° by recrystallization from an ether–benzene mixture and subsequent drying. The ester **15b** has infrared absorption[12] at 1692 cm.$^{-1}$ (conj. C=O) with an ultraviolet maximum[24] at 261 mμ (ϵ 11,000) as well as a point of inflection at 228 mμ (ϵ 14,800) and a series of n.m.r. peaks[39] in the region 2.0–3.0 τ (13H, aryl C—H) as well as a singlet at 3.30 τ [1H, CO(Ph)$CHSO_2$] and two singlets at 7.65 and 7.68 τ (6H, aryl CH_3).

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(37) A gas chromatographic column packed with silicone gum, no. SE-30, suspended on ground firebrick was employed for this analysis.

(38) A gas chromatographic column packed with Dow Corning silicone fluid, no. 550, suspended on ground firebrick was employed for this analysis.

(39) Determined as a solution in deuteriochloroform.

(40) The procedure of Z. Földi, *Ber.*, **60**, 656 (1927).

(41) R. Adams and L. M. Werbel, *J. Am. Chem. Soc.*, **80**, 5799 (1958).

Anal. Calcd. for $C_{22}H_{20}SO_4$: C, 69.45; H, 5.30; S, 8.43. Found: C, 69.38; H, 5.35; S, 8.41.

Reduction of an 87.7-mg. (0.23-mmole) sample of the tosyl ester **15b** with zinc and acetic acid as previously described afforded a quantitative yield (49.4 mg.) of the crude ketone **9b**, m.p. 100–104°. This ketone **9b**, which melted at 108.9–109.3° after recrystallization from ether, was identified with the previously described sample by a mixed melting point determination and comparison of infrared spectra. From a comparable Neber rearrangement employing 0.0154 mole of sodium methoxide and 0.0150 mole of the oxime tosylate **3b** in a mixture of 11 ml. of methanol and 96 ml. of benzene, the yields were: 22% keto amide **15b**, 13% tosyl ester **15b**, 19% ester **14a** ($R'' = CH_3$), and 18% amide **17b**.

The Neber Rearrangement of the Oxime Tosylate 3c.—A mixture of 6.6413 g. (0.0175 mole) of the oxime tosylate **4c**, 0.0184 mole of potassium ethoxide, and 38 ml. of ethanol was stirred at 0–5° for 4.5 hr. and then subjected to the usual isolation procedure. The product that was separated after acetylation of the basic fraction was 1.4667 g. (31.4%) of the keto amide **16c**, m.p. 76–80°, identified with the previously described sample by a mixed melting point determination and by comparison of infrared spectra and retention times.[37] The neutral fraction from this reaction contained[42] the ester **14c** ($R'' = C_2H_5$) a collected sample of which was identified with an authentic sample by comparison of retention times and infrared spectra. From a comparable reaction employing 5.6925 g. (0.015 mole) of the oxime tosylate **3c**, 0.0155 mole of sodium ethoxide, and 30 ml. of ethanol with a reaction time of 15 hr. at −3 to −1°, the keto amide **16c** (22%), the ester **14c** (1%), and the amide **17a** (1%) were calculated to be present employing the previously described analytical procedure. The residue initially separated from the reaction mixture was dissolved in acetic acid and then worked up as previously described to separate 486.1 mg. (12.1%) of the acetoxy ketone **18c** as white prisms from an ether–hexane mixture, m.p. 88–89.2°. Gas chromatographic analysis[37] of the mother liquors indicated that the total yield of this material was 52%.[43] The acetoxy ketone **18c** had infrared absorption[23] at 1743 cm.$^{-1}$ (ester C═O) and 1700 cm.$^{-1}$ (conj. C═O) with an ultraviolet maximum[24] at 247 mμ mμ (ε 13,600) and a series of n.m.r. peaks[23] in the region 2.0–3.1 τ (aryl C—H) with a singlet at 3.34 τ (1H, CO(Ar) CH—OCO—) and two singlets at 7.72 and 7.89 τ (6H, aryl and acetyl CH_3).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.33; H, 6.14.

Reduction of a 134.2-mg. sample of the acetoxy ketone with zinc and acetic acid as previously described gave, after recrystallization, 35.8 mg. (34%) of the ketone **9c**, m.p. 96–97°, identified with the previously described sample by a mixed melting point determination and comparison of infrared spectra.

Reaction of 5.6925 g. (0.0150 mole) of the oxime tosylate **3c** with 0.0166 mole of sodium methoxide in 96 ml. of benzene and 11 ml. of methanol for 15.5 hr. at 5° yielded, after the usual isolation and analytical procedure, the keto amide **16c** (21%), the ester **14c** ($R'' = CH_3$) (3%), the amide **17a** (0.2%), and the tosyl ester **15c** as 1.2976 g. (22.7%) of white prisms from an ether–benzene mixture, m.p. 76–80°. Recrystallization and subsequent drying gave the pure tosyl ester, m.p. 75.7–77.7°, with infrared absorption[23] at 1703 cm.$^{-1}$ (conj. C═O), an ultraviolet maximum[24] at 248.5 mμ (ε 13,000) with a point of inflection at 228 mμ (ε 15.900) and a series of n.m.r. peaks[39] in the region 2.0–3.0 τ (aryl CH) with a singlet at 3.33 τ (1H, $CO(Ar)CHOSO_2Ar$) and two singlets at 7.65 and 7.75 τ (6H, aryl CH_3).

Anal. Calcd. for $C_{22}H_{20}SO_4$: C, 69.45; H, 5.30; S, 8.43. Found: C, 69.22; H, 5.18; S, 8.01.

Reduction of a 190.2-mg. sample of the tosyl ester **15c** with zinc and acetic acid as previously described yielded 56.2 mg. (53.4%) of the ketone **9c**, m.p. 96.2–98°, identified by a mixed melting point determination and comparison of infrared spectra.

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(42) A column packed with General Electric silicone fluid, no. xF-1150, suspended on ground firebrick was employed for this analysis.

(43) Although the gas chromatograms of the corresponding fractions from the oxime tosylates **3a** and **3b** suggested the presence of small amounts of the corresponding acetoxy ketones **18**, the amounts present in these cases were too small to permit characterization.

Exchange Reactions of Deuterated Benzene Derivatives in Alkaline Medium. II. Deactivating Substituents[1-3]

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The rates of deuterium–protium exchange have been determined for benzene-*d*, toluene-2-*d*, -3-*d*, and -4-*d*, and *tert*-butylbenzene-2-*d* and -4-*d* in a liquid ammonia solution of potassium amide at 0°. An approximate determination of the rates of the heterogeneous exchange reactions of benzene-*d*, toluene -2-*d*, -3-*d*, and -4-*d*, and potassium phenoxide-2-*d*, -3-*d*, and -4-*d* with potassium amide in refluxing isopropylamine has also been made. In general, the substituted deuteriobenzenes react more slowly than deuteriobenzene itself. As all of these substituents have negative values of σ_I, the results support the previous interpretation of exchanges on the basis of the inductive effects of the substituents, resonance effects being of little importance.

An earlier investigation of the effect of substituents on the acidity of hydrogens located on benzene rings was made as a part of a study of the benzyne mechanism[5] of nucleophilic substitution of aryl halides.[1] The electronegative substituents, —F, —CF_3, and —OCH_3, increased the acidity, the effect being greatest at the 2-, less at the 3-, and least at the 4-position. These results were interpreted on the basis of the inductive effects[6] of the substituents.

The relative acidities of the hydrogens were determined by measuring the rate of replacement of deuterium by protium in the appropriate deuterated benzene derivative in the presence of a strong base, the amide ion, and a proton-donating solvent, refluxing liquid ammonia. When activating substituents were not present, the deuterium exchanged too slowly for convenient measurement so that the overriding importance of the inductive effect was not tested with deactivating substituents. An investigation of the effects of groups expected to be deactivating is reported in the present paper.

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(1) Part I, G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.*, **77**, 4540 (1955).

(2) M.A. thesis of E. M. L.; A. B. Honors Paper of E. L. J.

(3) This investigation was supported by a Frederick Gardner Cottrell grant from the Research Corporation. An equipment grant from the National Science Foundation made possible the purchase of the infrared spectrometer. Aid in the experimental work was provided by Miss Georgeanna Dean and Mrs. Eva G. Gans, who were supported by the Undergraduate Research Participation Program of the National Science Foundation.

(4) Joseph A. Skinner Fellow, 1960–1961.

(5) R. Huisgen, "Organometallic Chemistry," H. Zeiss, ed., Reinhold Publishing Corp., New York, N. Y., 1960, pp. 36–87.

(6) "Inductive effect" will be used in the sense which includes any field effect.