The Preparation of Decahydro- and Dodecahydro-4a-azachrysenes Related to Azasteroids[1a]

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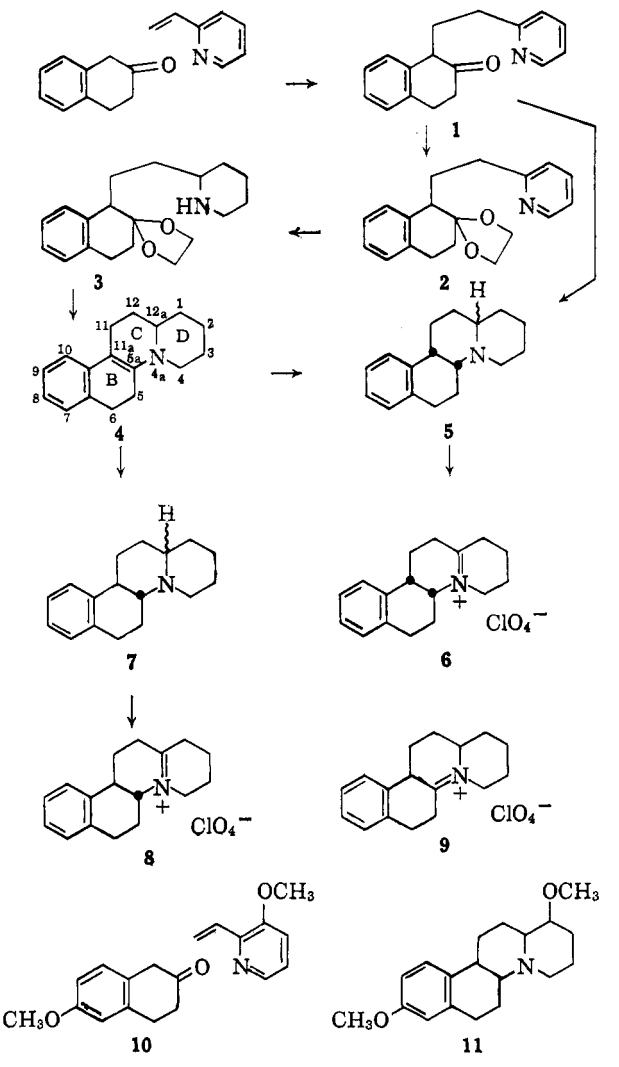
In a study designed to obtain azasteroids, the Michael addition of 2-tetralone to 2-vinylpyridine gave 1-(β-2-pyridylethyl)-2-tetralone (**1**) which on reduction of the pyridine ring gave the decahydro-4a-azachrysene **4**. Catalytic reduction of **4** gave a dodecahydro-4a-azachrysene formulated as **5** while sodium borohydride reduction of the perchlorate of **4** gave the isomeric dodecahydro-4a-azachrysene **7**. Mercuric acetate oxidation of **5** and **7** gave different enamine perchlorates (**6** and **8**, respectively), thus demonstrating a difference in the stereochemistry of the B–C ring fusion of **5** and **7** as well as the perchlorates. The synthesis of 3-methoxy-2-vinylpyridine is reported.

Because of the interest in the preparation of 4a-aza-D-homosteroids[2] we first concerned ourselves with the synthesis of 1,2,3,4,5,6,11,12,12a,4a-decahydro-4a-azachrysene (**4**) and then studied methods by which *trans* reduction of the Δ^{5a}-double bond could be accomplished. If such a reduction could be demonstrated, the remaining asymmetric center at position 12a should present no problem in the synthesis of a 17α-keto-14-aza-D-homosteroid (corresponds to a carbonyl group at position 1 of structure **4**). Such a steroid should be capable of equilibration to a product having the *trans-anti-trans* backbone configuration of naturally occurring steroids.

The Michael condensation of 2-tetralone with 2-vinylpyridine in dioxane in the presence of sodium hydride gave 1-(β-2-pyridylethyl)-2-tetralone (**1**) in 49% yield (55–64% based on recovered starting materials). A sample of this compound was reduced with lithium aluminum hydride giving one of the isomers of (β-2-pyridylethyl)-2-hydroxytetralin in 42% yield. The possibility of converting this substituted hydroxytetraline *via* its tosylate to a 5,6,11,11a,5a-hexahydro-4a-azaoniachrysene salt which, in turn, could be reduced selectively to other polyhydro-4a-azachrysenes was being considered. However, the early success of the method described below precluded further experimentation along these lines.

1-(β-2-Pyridylethyl)-2-ethylenedioxytetralone (**2**) was prepared in 66% yield from the sulfate salt of **1** by exchange with 2-methyl-2-ethyl-1,3-dioxolane. Hydrogenation of **2** in acetic acid–ethanol using Adams catalyst proceeded selectively and gave 77% of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone (**3**). Hydrolysis of the cyclic ethylene ketal grouping of **3** with hydrochloric acid followed by the addition of base resulted in the formation of the cyclic enamine **4** in 49–75% yields. The structure of the crystalline 1,2,3,4,-5,6,11,12,12a,4a-decahydro-4a-azachrysene (**4**) was substantiated by its ultraviolet absorption spectrum which is essentially the same as for 1-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline.[3] As in the case of this latter compound, treatment of the decahydro-4a-azachrysene **4** with methyl iodide resulted in a methiodide in which alkylation had occurred on nitrogen.[4,5] The infrared and ultraviolet spectra of the perchlorate of **4** indicate proton attachment chiefly on nitrogen.[6] (See Scheme I.)

SCHEME I



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(2) The synthesis of 8-azaestrone has appeared in a recent communication: R. I. Meltzer, D. M. Lustgarten, R. I. Stanaback, and R. E. Brown, *Tetrahedron Letters*, **23**, 1581 (1963).

(3) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(4) For other examples of carbon and/or nitrogen alkylation of enamines, see G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(5) The literature of enamines is reviewed in a chapter by J. Szmuszkovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Winberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1.

(6) Attachment of the proton to the β-carbon which might be expected in an enamine system[3-5] would, in this case, shift the double bond out of conjugation with the benzene ring.

1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (**4**) was reduced catalytically using Adams catalyst in ethanolic hydrochloric acid and also with palladium on charcoal in ethanol to 1,2,3,4,5,6,11,12,12a,4a,11a,5a-dodecahydro-4a-azachrysene (**5**). This same product was prepared by reductive cyclization of 1-(β-2-pyridylethyl)-2-tetralone (**1**) using Adams catalyst in ethanolic hydrochloric acid.

The stereochemistry of the B–C ring fusion of **5** is provisionally assigned as *cis* on the basis that catalytic hydrogenations of imines have given the *cis* isomer.[7] The relationship of the hydrogens at the *cis* B–C juncture with the C-12a hydrogen can either be *syn* or *anti*, more likely an equal mixture of the two. From the melting point spread of the perchlorate (m.p. 177–205°) it appears that indeed one deals with such a mixture. Mercuric acetate oxidation[5] of **5** gave a single product in the form of a new enamine[8] which was isolated as its perchlorate **6**. Such oxidations of amines occur by abstraction of a tertiary in preference to a secondary or primary hydrogen, α to the nitrogen.[5,9] Of the two possible tertiary perchlorates **6** and **9**, the latter is rejected because it would be expected to rearrange to the perchlorate of **4**. Since by destroying the asymmetry at C-12a oxidatively one gets a single isomer, it is concluded that the mixture of isomers in **5** is due to the relationship of the *cis*-hydrogens at C-11a and C-5a to the one at C-12a.

Attention was next turned to chemical reductions of the decahydro-4a-azachrysene **4** in an effort to produce compounds in which the hydrogens at C-11a and C-5a would have a *trans* relationship. Formic acid did not reduce **4**, starting material being isolated. However, the sodium borohydride reduction of the perchlorate of **4** gave a new amine (or a mixture of amines), **7** as a product, which had a different infrared spectrum from **5** as well as different derivatives. The derivatives (picrate m.p. 228–232°, perchlorate m.p. 231.5–233.5°) are not very sharp melting, indicating that small amounts of other isomers could be present. Mercuric acetate oxidation[5] of **7** gave a new enamine[8] as a single product isolated as its perchlorate, and assigned structure **8** on the basis of reasoning similar to that applied for structure **6**. Thus the elimination of the C-12a asymmetric center makes the enamine perchlorates **6** and **8** different only in the nature of the B-C ring juncture, and, since **6** has been provisionally assigned as the *cis* isomer, **8** is assigned as the *trans* isomer.

The Michael addition of 6-methoxy-2-tetralone to 3-methoxy-2-vinylpyridine followed by other chemical transformations of the product as described above in the model series would be expected to yield one or more 1,8-dimethoxydodecahydro-14-azachrysenes (**11**). Cleavage of the ether groups would be expected to give the corresponding dihydroxy compound which by appropriate chemical manipulations, should lead to 18-nor-D-homo-14-azaestrone and related steroids.

(7) The catalytic reduction of a mixture of 1-methyloctahydroquinolines has been reported to give *cis*-1-methyldecahydroquinoline; see N. J. Leonard, L. A. Milller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

(8) There are two possible enamines, one where the double bond is in the C and the other in the D ring.

(9) N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Croudhury, *J. Org. Chem.*, **21**, 344 (1956); N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955); N. J. Leonard, R. W. Fulmer, and A. S. Hay, *ibid.*, **78**, 3457 (1956).

6-Methoxy-2-tetralone is readily prepared[10]; however, a convenient synthesis of the unknown 3-methoxy-2-vinylpyridine had to be worked out. Methylation of 3-hydroxy-2-picoline with trimethylphenylammonium chloride[11] gave a mixture of 3-methoxy-2-picoline and dimethylaniline which was difficult to separate, and for this reason, methylation with diazomethane was used to obtain the desired product. Ethyl 3-methoxy-2-pyridylacetate was prepared by metalation of 3-methoxy-2-picoline with phenyllithium followed by carbonation and esterification.[12] Reduction of the ester with lithium aluminum hydride and dehydration of the resulting 2-hydroxyethyl-3-methoxypyridine with concentrated sodium hydroxide gave 3-methoxy-2-vinylpyridine. This latter material is fairly stable at room temperature, but tends to polymerize if distilled at temperatures much above 100°.

The condensation of 6-methoxy-2-tetralone and 3-methoxy-2-vinylpyridine appeared to proceed normally; however, this and other reactions leading to a functionalized 14-azasteroid have not been studied further.

Experimental[13]

1-(β-2-Pyridylethyl)-2-tetralone (**1**).—To a solution of 100 g. of 2-tetralone,[14] 200 ml. of dry dioxane, and 66.0 g. of redistilled 2-vinylpyridine was added 3 g. of sodium hydride. The mixture was stirred and refluxed for 16 hr. under a nitrogen atmosphere. Most of the dioxane was removed *in vacuo* and the residue was dissolved in excess dilute hydrochloric acid. Extraction of the aqueous solution with ether and distillation of the ether extract gave 13.0 g. of unchanged 2-tetralone, b.p. 90–92° (0.4 mm.). The acidic solution was rendered alkaline with sodium carbonate and extracted with ether. The dried ether extract was concentrated *in vacuo* and distilled giving 13 g. of unchanged 2-vinylpyridine, b.p. 40–45° (12 mm.), followed by 83.0 g. of 1-(β-2-pyridylethyl)-2-tetralone, b.p. 175–178° (0.02 mm.), and infrared absorption at 1710 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.25; H, 6.82; N, 5.57. Found: C, 81.20; H, 6.76; N, 5.67.

1-(β-2-Pyridylethyl)-2-tetralone picrate was obtained from ethanol quantitatively, m.p. 130–138°, and recrystallized from ethanol–acetonitrile, m.p. 132–140° (capillary m.p. 135–137°).

Anal. Calcd. for $C_{23}H_{20}N_4O_8$: C, 57.50; H, 4.19; N, 11.66. Found: C, 57.21; H, 4.21; N, 11.70.

1-(β-2-Pyridylethyl)-2-hydroxytetralin.—To a stirred solution of 0.76 g. of lithium aluminum hydride in 30 ml. of ether was added with stirring over a 30-min. period, 10.1 g. of 1-(β-2-pyridylethyl)-2-tetralone in 20 ml. of ether. The mixture was stirred for 1 hr., when the excess hydride was decomposed by the cautious addition of water followed by sodium bicarbonate. The product was extracted with ether and the dried ether extract was concentrated to give an oil which was crystallized from ethyl acetate–hexane yielding 4.2 g. of 1-(β-2-pyridylethyl)-2-hydroxytetralin, m.p. 78–81°, and infrared absorption at 3300 cm.$^{-1}$ (associated O–H).

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.78; H, 7.56; N, 5.32.

1-(β-2-Pyridylethyl)-2-ethylenedioxytetralone (**2**).—To a flask containing 24.0 g. (0.096 mole) of 1-(β-2-pyridylethyl)-2-tetralone was added slowly with stirring at 0°, 9.4 g. (0.096 mole) of con-

(10) N. A. Nelson, R. S. P. Hsi, J. M. Schuck, and L. D. Kahn, *ibid.*, **82**, 2573 (1960).

(11) B. R. Baker and F. J. McEvoy, *J. Org. Chem.*, **20**, 136 (1955).

(12) *Cf.* R. B. Woodward and E. C. Kornfeld, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 413.

(13) Melting points were determined using a hot-stage microscope and are corrected. Boiling points are uncorrected. The infrared spectra were determined in carbon tetrachloride unless otherwise stated with a Baird, Model B, or a Perkin-Elmer, Model 21 or 137, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(14) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

centrated sulfuric acid followed by 75 ml. of redistilled 2-methyl-2-ethyl-1,3-dioxolane and 1 g. of *p*-toluenesulfonic acid. The flask, equipped with a short Vigreux column, was immersed in an oil bath at 125–130° while 2-butanone was collected by distillation. When the ketone ceased to distill, the excess 2-methyl-2-ethyl-1,3-dioxolane was distilled and the solid residue was treated with excess 10% methanolic potassium hydroxide solution. The product was extracted with benzene and the extract was washed with water and concentrated *in vacuo*. Distillation of the residue gave 18.7 g. of a light yellow liquid, b.p. 165–185° (0.005 mm.), and no carbonyl infrared absorption. The analytical sample of 1-(β-2-pyridylethyl)-2-ethylenedioxytetralone had b.p. 161–162° (0.002 mm.).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.27; N, 4.98.

The **oxalate** derivative was prepared in ethanol and precipitated with hexane, m.p. 107.5–109.5°.

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.32; H, 6.32; N, 3.46.

1-(β-2-Piperidylethyl)-2-ethylenedioxytetralone (3).—A solution of 18.6 g. of 1-(β-2-pyridylethyl)-2-ethylenedioxytetralone in 100 ml. of absolute ethanol and 30 ml. of glacial acetic acid was hydrogenated at an initial pressure of 30 p.s.i. in the presence of 0.3 g. of platinum oxide. After 18 hr. the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was rendered alkaline with a 10% methanolic potassium hydroxide solution. The mixture was concentrated *in vacuo* and the residue was diluted with benzene. The benzene solution was washed with water and distilled giving 14.6 g. of product, b.p. 164° (0.005 mm.). As expected, the product showed no carbonyl or substituted pyridine absorption near 1710 and 1600 cm.$^{-1}$, respectively.

The **oxalate** of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone was formed in ethanol, precipitated with hexane, and recrystallized from ethanol–hexane, m.p. 158–160°.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.47; H, 7.62; N, 3.80.

1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (4).—A solution of 40.0 g. of 1-(β-2-piperidylethyl)-2-ethylenedioxytetralone (**3**) in 180 ml. of 6 *N* hydrochloric acid was stirred for 10 hr. at room temperature under a nitrogen atmosphere. The solution was made basic with sodium hydroxide and extracted with benzene. The benzene extract was concentrated *in vacuo* and the residue distilled giving 24.9 g. of material, b.p. 152–168° (0.02 mm.), which on trituration with ethanol gave crystalline material. The product was recrystallized from ethanol–water giving 16.0 g. of **4**, m.p. 57–58.5°; infrared absorption at 1615, 1698, and 1565 cm.$^{-1}$ (conjugated C=C and aromatic ring), and ultraviolet maxima at 236 mμ (ε 8600) and 313 (10,030).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.85; N, 5.85. Found: C, 85.30; H, 8.99; N, 5.97.

A **perchlorate of 4** was formed in ether and recrystallized from ethanol, m.p. 184–185°, infrared maximum at 1642 cm.$^{-1}$ (KBr disk), and an ultraviolet maximum at 251 mμ (ε 8150).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 60.01; H, 6.58; N, 3.98.

A **methiodide of 4** was prepared in methyl iodide and recrystallized from ethyl acetate–ethanol, m.p. 184–185°, ultraviolet maxima 215 mμ (ε 39,000), 221 (32,600), and 259 (11,850).

Anal. Calcd. for $C_{18}H_{24}IN$: C, 56.70; H, 6.34; N, 3.74. Found: C, 56.82; H, 6.08; N, 3.90.

1,2,3,4,5,6,11,12,12a,4a,11a,5a-Dodecahydro-4a-azachrysene (5). A. From 1-(β-2-Pyridylethyl)-2-tetralone (1).—Platinum oxide catalyst (0.25 g.) was added to a solution of 10.3 g. of 1-(β-2-pyridylethyl)-2-tetralone, 35 ml. of ethanol, and 12 ml. of concentrated hydrochloric acid. The mixture was hydrogenated at an initial pressure of 30 p.s.i. After 12 hr. the theoretical amount of hydrogen had been absorbed and the mixture was filtered. The filtrate was concentrated somewhat, rendered alkaline with sodium hydroxide, and extracted with benzene. Concentration of the benzene extract and distillation of the residue gave 8.02 g. of product, b.p. 106–108° (0.001 mm.), ultraviolet maxima at 267 mμ (ε 500) and 274 (500) with a shoulder at 260 (400). The infrared spectrum of the product showed the absence of hydroxyl, carbonyl, and substituted pyridine chromophores.

Anal. Calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 83.72; H, 9.81; N, 5.62.

A **picrate of 5** was formed essentially in quantitative yield in absolute ethanol, m.p. 257–259°, and on recrystallization from ethanol–acetonitrile melted at 260–262° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_7$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.96; H, 5.82; N, 11.68.

A **methiodide of 5** was formed in methyl iodide and recrystallized from ethanol–hexane, m.p. 270–271°.

Anal. Calcd. for $C_{18}H_{26}IN$: C, 56.54; H, 6.85; N, 3.66. Found: C, 56.39; H, 6.76; N, 3.72.

A **perchlorate of 5** was formed in ether essentially quantitatively, m.p. 177–205°, and, after repeated recrystallizations from ethanol–hexane, it melted at 178–208°.

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.18; N, 4.10. Found: C, 59.83; H, 7.26; N, 4.04.

B. From 1,2,3,4,5,6,11,12,12a,4a-Decahydro-4a-azachrysene (4).—A mixture of 0.60 g. of **4**, 8 ml. of ethanol, 2 ml. of concentrated hydrochloric acid, and 0.04 g. of platinum oxide was hydrogenated at atmospheric pressure. The theoretical amount of hydrogen was absorbed in 90 min. The catalyst was removed, the filtrate was rendered alkaline and shaken with benzene and water, and the benzene layer was concentrated. The residue was converted essentially quantitatively to the picrate, m.p. 262–263° dec. A mixture melting point with the picrate prepared in part A was undepressed.

Hydrogenation of 1.5 g. of **4** in 15 ml. of absolute ethanol with 0.10 g. of 10% palladium on charcoal was complete in 7 hr. The catalyst was removed and the filtrate was concentrated, then distilled giving material identical with the spectrum of the dodecahydro-4a-azachrysene **5** prepared as described in part A. The picrate formed in ethanol had m.p. 262–263° dec. (undepressed with the samples of this material described above).

1,2,3,4,5,6,11,12,11a,5a-Decahydro-4a-azachrysene Perchlorate (6).—A solution of 2.61 g. of 1,2,3,4,5,6,11,12,12a,4a,11a,-5a-dodecahydro-4a-azachrysene (**5**), 14.0 g. of mercuric acetate, and 70 ml. of 5% aqueous acetic acid was heated on the steam bath for 2 hr. The precipitated mercurous acetate (5.0 g., 89%) was removed and the filtrate was saturated with hydrogen sulfide. The mixture was filtered, the filtrate was rendered alkaline with sodium hydroxide, and the product was extracted with ether. The ether extract was concentrated to about 20 ml. and treated with 1 ml. of 72% perchloric acid to give 2.5 g. of a perchlorate which on recrystallization from ethanol afforded 1.7 g. of product, m.p. 217.5–218.5°, ultraviolet maxima at 265 mμ (ε 680) and 272 (715), and infrared maximum at 1670 cm.$^{-1}$ (C=N$^+$) (KBr pellet).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 60.16; H, 6.58; N, 4.33.

The free base corresponding to **6** was obtained by treating the perchlorate **6** with 10% aqueous sodium hydroxide. The crude product was extracted with benzene and distilled through a Hickmann apparatus to give the enamine, m.p. 50.5–54.5° with previous softening, and infrared maximum at 1650 cm.$^{-1}$ (C=C) (in $CHCl_3$).

1,2,3,4,5,6,11,12,12a,4a,11a,5a-Dodecahydro-4a-azachrysene (7).—A stirred solution of the perchlorate salt of 1,2,3,4,5,6,11,-12,12a,4a-decahydro-4a-azachrysene (**4**) in 45 ml. of methanol was treated cautiously with 4.0 g. of sodium borohydride. When the addition was complete, the mixture was stirred under reflux for 1 hr. The mixture was concentrated, rendered alkaline with sodium hydroxide solution, and extracted with benzene. The benzene extract was concentrated and the residue was distilled through a semimicro column giving 0.90 g. of product, b.p. 106–109° (0.001 mm.). The infrared spectrum of this material is similar to but not identical with the isomer **5**.

The **picrate** of **7** was obtained in the usual way and recrystallized from ethanol, m.p. 228–232° dec. (softening at 225°).

Anal. Calcd. for $C_{23}H_{26}N_4O_7$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.70; H, 5.77; N, 12.02.

A **methiodide** of **7** was prepared in methyl iodide and recrystallized from ethanol–hexane, m.p. 276.5–277.5°.

Anal. Calcd. for $C_{18}H_{26}IN$: C, 56.54; H, 6.85; N, 3.66. Found: C, 56.59; H, 6.92; N, 3.68.

The **perchlorate** of **7** was formed in ether and recrystallized from ethanol, m.p. 231.5–233.5°.

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.08; N, 4.10. Found: C, 59.80; H, 7.22; N, 4.09.

1,2,3,4,5,6,11,12,11a,5a-Decahydro-4a-azachrysene Perchlorate (8).—Following the procedure described above for the preparation of the isomer **6**, 2.45 g. of 1,2,3,4,5,6,11,12,12a,4a,-11a,5a-dodecahydro-4a-azachrysene (**5**) in a solution of 13.0 g. of

mercuric acetate and 60 ml. of 5% aqueous acetic acid was converted to 1.75 g. of perchlorate **8**, m.p. 233.5–235.5°, infrared maximum 1670 cm.$^{-1}$ (C=N$^+$) (in KBr pellet) and ultraviolet maxima at 264 mμ (ε 1200) and 272 (1200). A mixture melting point of this material with the perchlorate **6** was depressed (m.p. 202–205°).

Anal. Calcd. for $C_{17}H_{22}ClNO_4$: C, 60.08; H, 6.53; N, 4.12. Found: C, 59.78; H, 6.28; N, 4.36.

A portion of the perchlorate **9** was converted to the corresponding enamine using sodium hydroxide. Distillation of the product through a Hickmann apparatus and trituration of the distillate with a drop of ethanol gave material with m.p. 74.5–76.5° and infrared maximum at 1650 cm.$^{-1}$ (C=C) (in chloroform).

3-Methoxy-2-picoline.—To a stirred solution of 26 g. of diazomethane in 2 l. of ether cooled to 5° was added dropwise over a 30-min. period 60 g. of 3-hydroxy-2-picoline in 500 ml. of butanol. With continued stirring overnight, the temperature of the solution was allowed to rise to room temperature. The solution was distilled through a short Vigreux column and gave 31 g. of 3-methoxy-2-picoline, b.p. 84.5–85.5° (17 mm.), n^{28}D 1.5128, ultraviolet maxima at 221 mμ (ε 7150) and 279 (5400), and picrate derivative m.p. 166–168° (lit.[13] m.p. 167–168°). The residue from the distillation was crystallized from an acetonitrile–hexane mixture and gave 13.0 g. of unchanged 3-hydroxy-2-picoline, m.p. 167–169° (lit.[15] m.p. 170–171°).

Ethyl 3-Methoxy-2-pyridylacetate.—To a solution of phenyllithium prepared from 5.0 g. of lithium wire, 400 ml. of ether, and 56.3 g. of bromobenzene was added with stirring 44.0 g. of 3-methoxy-2-picoline over a 45-min. period. The red solution was treated with excess Dry Ice. The mixture was allowed to stand overnight and the ether was then removed *in vacuo*. Absolute ethanol (300 ml.) was added to the solid and, while the mixture was cooled in an ice bath, a saturated solution of ethanolic hydrogen chloride was added dropwise with stirring until the mixture was strongly acidic. The mixture was allowed to stand for 10 hr. at room temperature when most of the ethanol was removed *in vacuo* and 400 ml. of chloroform was added. The chloroform solution was stirred with a paste of 110 g. of potassium carbonate and 65 ml. of water for 30 min., then filtered. The filtrate was washed with water, concentrated, and distilled to give 17.7 g. of 3-methoxy-2-picoline, b.p. 85–87° (18 mm.), and 20.8 g. of ethyl 3-methoxy-2-pyridylacetate, b.p. 94.0–94.5° (0.5 mm.), n^{21}D 1.5038, and infrared maximum at 1730 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.77; N, 7.34.

The **picrate** derivative was obtained from ethanol and melted at 156–158°.

Anal. Calcd. for $C_{16}H_{16}N_4O_{10}$: C, 45.29; H, 3.80; N, 13.21. Found: C, 45.32; H, 4.01; N, 13.24.

2-Hydroxyethyl-3-methoxypyridine.—To a stirred solution of 800 ml. of ether and 8.3 g. of lithium aluminum hydride was added dropwise 37.0 g. of ethyl 3-methoxy-2-pyridylacetate. After 1 hr., 8.3 ml. of water was added cautiously followed by 8.3 ml. of 15% sodium hydroxide solution and 25 ml. of water. The ether solution was filtered, dried, and concentrated giving 27.5 g. of product with m.p. 76–80° and infrared maximum at 3340 cm.$^{-1}$ (associated O–H). The analytical sample was recrystallized from hexane–ethyl acetate, m.p. 79–80°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.96; H, 7.37; N, 9.28.

The **picrate** derivative was prepared in ethanol and had m.p. 146–149°.

Anal. Calcd. for $C_{14}H_{14}N_4O_9$: C, 43.98; H, 3.69; N, 14.66. Found: C, 44.03; H, 3.61; N, 14.90.

3-Methoxy-2-vinylpyridine (12).—To 150 ml. of 50% sodium hydroxide solution heated to reflux was added dropwise a solution of 6.5 g. of 2-hydroxyethyl-3-methoxypyridine in 25 ml. of water. The product steam distilled from the reaction mixture. The distillate was extracted with ether and the ether extract was dried over sodium hydroxide. Distillation of the solution gave 3.5 g. of 3-methoxy-2-vinylpyridine, b.p. 60–62° (0.5 mm.), n^{23}D 1.5600, and ultraviolet maxima at 237 mμ (ε 9850) and 308 (7000).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.30; H, 6.96; N, 10.58.

The **picrate** derivative was obtained from ethanol, m.p. 139–141° (softened at 132°).

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.25; H, 3.30; N, 15.34.

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(15) H. Rapoport and E. J. Volcheck, Jr., *J. Am. Chem. Soc.*, **78**, 2451 (1956), and references contained therein.

Studies on the Base Strengths of N,N-Disubstituted Amides

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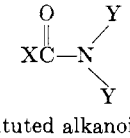
The carbonyl stretching vibration frequencies were determined for a series of N,N-disubstituted alkanoic acid amides and closely related compounds in dilute solution in isooctane ($\gamma_{C=O(iso)}$) and in chloroform ($\gamma_{C=O(HCCl_3)}$). pK_a values were determined by potentiometric titration in dilute nitromethane solution using perchloric acid as titrant. A linear relationship was found between $\gamma_{C=O(iso)}$ and $\Sigma\sigma^*$, where σ^*-values for X were the Taft polar factors, and σ^*-values for NY_2 were empirically estimated. A linear relation was also observed between pK_a and σ^* for the N,N-disubstituted formamides and acetamides but not for the N,N-disubstituted propionamides. With chloroform as the electron acceptor, relative base strengths were measured by $\Delta\gamma_{C=O}/\gamma_{C=O(iso)}$, where $\Delta\gamma_{C=O}$ was $\gamma_{C=O(iso)} - \gamma_{C=O(HCCl_3)}$. In this case, an increase in $\Delta\gamma_{C=O}/\gamma_{C=O(iso)}$ with increase in $\Sigma\sigma^*$ was observed only for the formamides. Using published data for log K_{assn} with phenol as the acid, $\Sigma\sigma^*$-log K_{assn} relationships were obtained which were intermediate to those using perchloric acid and chloroform. These results permitted an analysis of the variable steric effects in the free base and in the associated complexes. The order of steric requirements was found to be perchloric acid < phenol < chloroform. Evidence is presented that relief of steric strains in these complexes occurs through twisting about the C–N bond.

We have been concerned with various Lewis bases in nonaqueous systems and how the base strength relates to structure. Toward this end, spectroscopic and potentiometric titration measurements were made on



N,N-Disubstituted alkanoic acid amides

a series of N,N-disubstituted alkanoic acid amides and closely related compounds in dilute solution, using perchloric acid and chloroform as electron acceptors. The relative base strengths were compared with literature values using phenol and also iodine as electron acceptors.

The general approach and results are presented in the next section and in Tables I–III. This is followed by a discussion of the base strength parameters and an