Synthesis and Structure of 7-Methyl- and 7-Phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-ones

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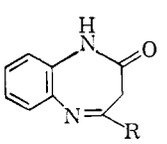
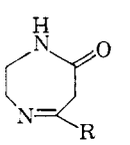
The condensation of ethylenediamine with ethyl benzoylacetate gave the phenyltetrahydrodiazepinone Xb, whereas ethyl acetoacetate gave only the bisenamine III. The synthesis of the analogous methyltetrahydrodiazepinone Xa is described.

The condensation of *o*-phenylenediamine with β-keto esters has been studied by several groups of investigators.[1–5] In the case of ethyl acetoacetate the reaction has yielded several products, among them, the benzodiazepinone Ia. Ethyl benzoylacetate was reported to give a single product, the benzodiazepinone Ib.[2] Convincing evidence, both chemical and spectral, has been adduced in support of both Ia[4,5] and Ib.[2,5] Analogous condensations of ethylenediamine with ethyl acetoacetate and ethyl benzoylacetate were reported by Ried and Höhne[6] to yield the corresponding tetrahydrodiazepinones IIa and IIb. Only analytical data was offered in support of these structures. Because of our interest in simple 1,2,3,4-tetrahydro-1,4-diazepin - 5 - ones as possible pharmacodynamic agents and the existence of subsequent reports conflicting with the structural assignments made[7,8] we were led to re-examine the work of Ried and Höhne.

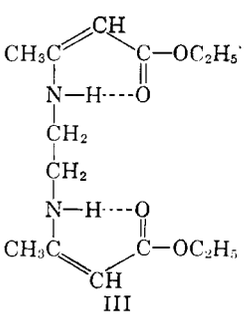
When the reaction of ethylenediamine with acetoacetic ester was repeated under the conditions described,[6] a solid of about the same melting point was obtained. However, the molecular formula calculated from the analytical data, $C_{14}H_{24}N_2O_4$, clearly excluded structure IIa. Strong bands at 6.08 and 6.22 μ in the infrared and at



Ia. R = CH_3
Ib. R = C_6H_5

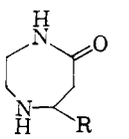


IIa. R = CH_3
IIb. R = C_6H_5

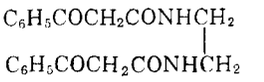


III

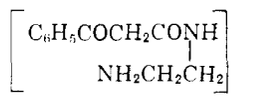
293 (ε 32,100) and 280 mμ (ε 31,100) in the ultraviolet provided strong arguments for the hydrogen-bonded bisenamine structure III. This data is in accord with that of Martell, *et al.*,[7] as well as with that of Dudek and Holm.[8] A number of modifications of the reaction conditions were performed, but the sole product isolated in each instance was III.



IVa. R = CH_3
IVb. R = C_6H_5



V



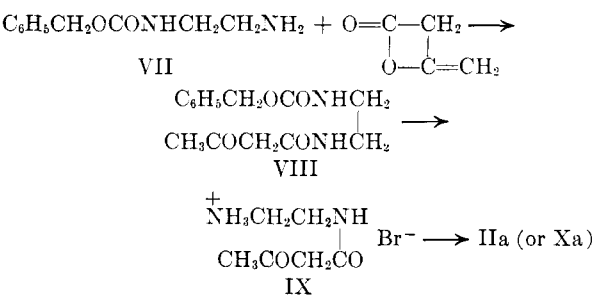
VI

On the other hand, a repetition of the reaction of ethyl benzoylacetate with ethylenediamine under the conditions given by Ried and Höhne[6] (heating the components in the presence of acetic acid) furnished a solid whose molecular formula, $C_{11}H_{12}N_2O$, calculated from analytical data on the base, the monohydrochloride, and the monopicrate, fitted the proposed tetrahydrodiazepinone structure IIb (or its tautomer Xb). Further support for IIb (Xb) was provided by a molecular weight determination (isothermal distillation) and the absorption of one mole of hydrogen in the presence of palladium on charcoal to yield the hexahydrodiazepinone IVb. When the reaction conditions were modified (heating the components in xylene in the absence of acetic acid), a second product was isolated along with IIb. Analytical and spectral data indicated that this was simply the bisamide V. There was no indication of bisenamine formation analogous to that observed in the case of acetoacetic ester. Presumably, the lower reactivity of a benzoyl carbonyl group in comparison to an acetyl carbonyl group is sufficient to account for the striking differences observed for the course of these reactions. The formation of IIb (Xb) appears to require initial attack by ethylenediamine on ethyl benzoylacetate to give VI (not isolated). In turn, VI can attack a second molecule of ethyl benzoylacetate to give V or attack

(1) W. A. Sexton, *J. Chem. Soc.*, 303 (1942).
(2) W. Ried and P. Stahlhofen, *Ber.*, **90**, 828 (1957).
(3) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1046 (1960).
(4) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *ibid.*, **43**, 1298 (1960).
(5) J. Davoll, *J. Chem. Soc.*, 308 (1960).
(6) W. Ried and W. Höhne, *Ber.*, **87**, 1811 (1954).
(7) A. E. Martell, R. Linn Belford, and M. Calvin, *J. Inorg. Nucl. Chem.*, **5**, 170 (1958).
(8) G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099 (1961).

the ketone carbonyl group intramolecularly to give the tetrahydrodiazepinone IIb (Xb).

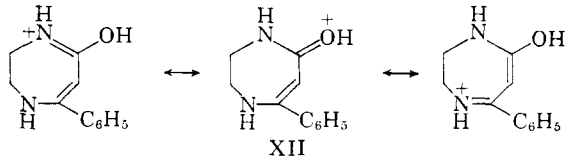
A synthesis of the methyl analog IIa (or its tautomer Xa) was then carried out in the following manner:



The monobenzyloxycarbonyl derivative VII was prepared by Schotten-Baumann acylation of ethylenediamine with benzyl chloroformate under conditions used by Goldman and Williams[9] for monoacylation of piperazine. Condensation of VII with diketene gave the crystalline mixed amide VIII. Removal of the benzyloxycarbonyl group with hydrobromic-acetic acids gave the salt IX as a very hygroscopic solid, which, on treatment with ammonia in chloroform, gave the desired tetrahydrodiazepinone IIa (Xa) as a solid whose m.p. is about 35° higher than that reported.[6] Support for structure IIa (Xa) was given by analysis and molecular weight determination by mass spectrometry. Catalytic hydrogenation gave the hexahydrodiazepinone IVa. Examination of the ultraviolet and infrared spectral data compels the assignment of the tetrahydrodiazepinone structure as the enamine tautomer Xa rather than the ketimine IIa. The band at 6.14 μ is reasonably assigned to the C=O stretching vibration of an α,β-unsaturated amide. In the reduced compound IVa the amide C=O is shifted to 6.00 μ. In the ultraviolet spectrum of Xa a maximum at 285 mμ (ϵ 15,900) is noted. Glickman and Cope[10] have observed λ_{max}^{EtOH} 284 mμ (ϵ 32,400) for ethyl β-methylaminocrotonate. What is particularly striking is that protonation of Xa results in the disappearance of absorption above 220 mμ in the ultraviolet spectrum. This fact is best interpreted as protonation on the 6-carbon atom to give the unconjugated cation XI.[11]

Xa. R = CH_3
Xb. R = C_6H_5

XI



XII

The assignment of the enamine structure Xb rather than the ketimine IIb for the 7-phenyl analog is preferable although the problem is more complex. On the one hand the band at 6.14 μ is reasonably located for the C=O group of an α,β-unsaturated amide, as is the shift to 6.01 μ in the reduced base IVb. In the ultraviolet spectrum, however, maxima at 228 (ϵ 15,300) and 304 mμ (ϵ 13,200) for the base Xb are shifted to 244 (ϵ 11,000) and 318 mμ (ϵ 16,800) on salt formation. Protonation on the 6-carbon or on the 1-nitrogen atom is not indicated by this shift. Since structure Xb can be regarded as a vinylogous amide and the accumulated evidence indicates that protonation of amides occurs at the oxygen atom,[12] a reasonable alternative is protonation on oxygen as indicated by XII. The cation XII would be expected to be resonance-stabilized by contributing forms in which each of the hetero atoms and the benzene ring bear a part of the positive charge.

Independent support for the enamine structure Xb was provided by the n.m.r. spectrum[13] taken in CD_3SOCD_3 which shows a sharp peak at 2.55 τ (phenyl protons), a broad peak at 2.7–3.0 τ (NH protons), and a single peak at 5.43 τ (—C(=O)—NH— or =C— protons). The area obtained by electronic integration of the curve shows a ratio of approximately 7:1 for combined phenyl and NH protons to olefinic proton. Addition of CD_3OD to the CD_3SOCD_3 solution caused the virtual elimination of the resonance at 2.7–3.0 τ. The area under the curve now showed a ratio of about 5:1 for phenyl protons to olefinic proton, corresponding to the loss of two NH protons by deuterium exchange. These results are in accord with structure Xb and not with tautomer IIb, which requires ratios of 6:2 and 5:2, respectively.

Experimental

Absorption Spectra.—The ultraviolet absorption spectra were determined in methanol with a Cary 11 spectrophotometer. The infrared spectra were taken in chloroform, unless otherwise stated, with a Perkin-Elmer Infracord.

Melting Points.—Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected.

Diethyl 3,3′-(Ethylenediimino)dicrotonate (III).—When a mixture of 6 g. (0.1 mole) of ethylenediamine, 13 g. (0.1 mole) of acetoacetic ester, and 5 ml. of acetic acid was heated in a bath at 130° for 1 hr. in accordance with the procedure of Ried and Höhne,[6] there was obtained on work-up

(9) L. Goldman and J. H. Williams, *J. Org. Chem.*, **18**, 815 (1953).

(10) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(11) For a discussion of the β-carbon protonation of enamines see N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

(12) For a review of the evidence, see A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).

(13) The n.m.r. spectrum was determined with a Varian Associates A-60 spectrometer at 60 Mc.

12.2 g. (86%) of a white solid, m.p. 115–122°. After two recrystallizations from methanol there was obtained 7.9 g. (56%) of product, m.p. 125–127°; λ_{max} 293 (ϵ 32,100) and 280 mμ (ϵ 31,100). The infrared spectrum showed bands at 6.08 and 6.22 μ. Martell, *et al.*,[7] report bands at 5.78 (weak), 6.08, and 6.22 μ in a mineral oil mull. Ried and Höhne[6] report m.p. 129.5°.

Anal. Calcd. for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 59.01; H, 8.11; N, 9.79.

When a solution of 15.3 g. (0.118 mole) of acetoacetic ester and 6 g. (0.1 mole) of ethylenediamine in 100 ml. of xylene was refluxed for 1 hr. using a water separator, there was obtained after one recrystallization from methanol 4.3 g. (30%) of III, m.p. 124–126°. No other product was isolated.

Diethyl 3,3′-(Ethylenediimino)bis(2-methylcrotonate).—A solution of 7.2 g. (0.05 mole) of ethyl α-methylacetoacetate and 3 g. (0.05 mole) of ethylenediamine was warmed on a steam bath for 10 min. and then cooled slowly. The oily mass was dissolved in hot ethanol and the solution was diluted with water. The product separated as a white solid. One recrystallization from ethanol gave 4.1 g. (53%) of the product, m.p. 101–103°; λ_{max} 297 (ϵ 25,600) and 308 mμ (ϵ 26,100). The infrared spectrum showed bands at 6.09 and 6.27 μ.

Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.33; H, 9.22; N, 8.91.

Robinson[14] prepared the corresponding dimethyl ester from methyl α-methylacetoacetate and ethylenediamine.

Reaction of Ethylenediamine with Ethyl Benzoylacetate; Preparation of 7-Phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one (Xb) and N,N′-ethylenebis(2-benzoylacetamide) (V).—When a solution of 9.6 g. (0.05 mole) of benzoylacetic ester, 3 g. (0.05 mole) of ethylenediamine, and 5 ml. of acetic acid was heated in a bath at 120° for 75 min. in accordance with the procedure of Ried and Höhne,[6] there was isolated on work-up only the tetrahydrodiazepinone Xb in 6% yield, m.p. 206–209°.

A more satisfactory procedure is as follows: A solution of 19.2 g. (0.1 mole) of benzoylacetic ester and 10 ml. of xylene was added, dropwise, over 40 min., to a refluxing solution of 6.0 g. (0.1 mole) of ethylenediamine and 100 ml. of xylene. Refluxing was continued for 1 hr. with a water separator. During this time an oily layer separated. On cooling, the oil solidified to a hard mass. The xylene layer was decanted and discarded. The solid was suspended in about 100 ml. of chloroform and the mixture was filtered. The chloroform filtrate was worked up in the manner described below. The solid was recrystallized from ethanol to give 3.1 g. (17%), of 7-phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one (Xb), m.p. 206–209°. One more recrystallization gave the analytical sample, m.p. 207–209°. Ried and Höhne[6] report m.p. 209–210°. The spectral data are as follows: ultraviolet, λ_{max} 228 (ϵ 15,300) and 304 mμ (ϵ 13,200); λ_{max}^{acid} 244 (ϵ 11,000) and 318 mμ (ϵ 16,800); infrared (oil mull), 6.14, 6.30 (shoulder), and 6.47 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88; mol. wt., 188. Found: C, 69.36, 69.99, 69.66; H, 6.38, 6.43, 6.50; N, 15.35, 15.09; mol. wt., 195 (isothermal distillation).

The picrate of Xb crystallized from ethanol, m.p. 178–179°.

Anal. Calcd. for $C_{17}H_{15}N_5O_8$: C, 48.92; H, 3.62; N, 16.78. Found: C, 49.24; H, 3.69; N, 17.20.

The hydrochloride was prepared by treatment of Xb with ethanolic hydrogen chloride, m.p. 211.5–213.5° dec.

Anal. Calcd. for $C_{11}H_{13}ClN_2O$: C, 58.79; H, 5.83; Cl, 15.78; N, 12.47. Found: C, 58.82; H, 6.04; Cl, 15.80; N, 12.44.

The aforementioned chloroform filtrate was treated with ether. The oil which separated was triturated with several portions of ether, whereupon it solidified. After three recrystallizations from ethanol, 1.7 g. (10%) of N,N′-ethylenebis(2-benzoylacetamide) (V) was obtained as white crystals, m.p. 166.5–167.5°. The spectral data are as follows: ultraviolet,[15] λ_{max} 244 (ϵ 23,600) and 287 mμ (ϵ 7400); infrared, 2.95, 3.13, 5.91, 6.10, and 6.36 μ.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.62, 67.95, 67.82; H, 5.78, 5.92, 5.86; N, 8.24.

Hexahydro-7-phenyl-1,4-diazepin-5-one (IVb).—A solution of 3.76 g. (0.02 mole) of Xb in 150 ml. of ethanol was treated with 1 g. of palladium–charcoal catalyst (5%) and reduced with hydrogen at 40° and 33 p.s.i. After 7 hr., the mixture was cooled and filtered. Evaporation of the filtrate gave the base as an oily residue. This was dissolved in ethanol and treated with ethanolic hydrogen chloride and ether. The resulting crystalline hydrochloride of IVb melted at 217–221° dec.; yield: 1.75 g. (39%). The analytical sample was obtained after two recrystallizations from ethanol, m.p. 229–230° dec. The infrared spectral data (oil mull) are: 2.92, 5.99, and 6.31 μ.

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.26; H, 6.67; Cl, 15.64; N, 12.36. Found: C, 58.04; H, 6.76; Cl, 15.60; N, 12.43.

The free base (IVb) was liberated from the hyrochloride by means of ammonia in chloroform. After one recrystallization from benzene–petroleum ether, its m.p. was 105.5–106.5°. The infrared spectrum showed bands at 2.90, 3.10, and 6.01 μ.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.16; H, 7.60; N, 14.50.

Benzyl (2-Aminoethyl)carbamate (VII).—A mixture of 60 g. (1 mole) of ethylenediamine, 250 ml. of water, 500 ml. of methanol, and 30 ml. of 0.04% Bromophenol Blue solution was acidified to pH 3 (yellow color) with 165 ml. of 12 *N* hydrochloric acid. The resulting solution was cooled to 25° and, while being vigorously stirred, 100.6 g. (0.59 mole) of benzyl chloroformate was added dropwise and 210 ml. of 5 *N* sodium hydroxide was added as required to maintain the solution at pH 3.0–4.5 (addition time 1.75 hr.). The methanol was removed at reduced pressure and the reaction mixture was filtered to remove 7.7 g. of dibenzyl ethylenedicarbamate, which melted at 165–167° after one recrystallization from alcohol. Linstead, *et al.*,[16] report m.p. 166.5°. The aqueous filtrate was then extracted once with benzene and the benzene extract was discarded. The aqueous solution was cooled in a salt–ice bath, layered with ether, and treated with 130 ml. of 10 *N* sodium hydroxide to pH 12–13. Three layers formed: an ether layer, an aqueous layer, and a blue oily layer. The aqueous layer was separated and extracted four times with portions of ether. The ether layer and ether extracts were combined with the blue oily layer and the ether was removed using a water pump; then an oil pump was used at 25° until the pressure dropped to 0.6 mm. During this time water and ethylenediamine distilled. The residue left in the flask consisted of an oil and a small amount of solid. After the mixture was filtered through a sintered glass funnel to remove the solid impurity, there was obtained 61.8 g. (54%) of VII. This crude oil worked satifactorily in the next step without purification.

It was found that distillation of VII at reduced pressure or prolonged standing at room temperature led to some decomposition with the formation of benzyl alcohol (b.p. 60°/0.6 mm.), identified by comparison of infrared spectral data with an authentic sample, and ethyleneurea (m.p. 129–131°), identified by infrared data and a mixed m.p. determination with an authentic sample.

Benzyl (2-Acetoacetamidoethyl)carbamate (VIII).—A solution of 9 g. (0.046 mole) of undistilled VII in 100 ml. of ether and a solution of 4.2 g. (0.05 mole) of diketene in 100

(14) R. Robinson, *J. Chem. Soc.*, **109**, 1038 (1916).

(15) Ethyl benzoylacetate shows λ_{max} 244 (ϵ 11,000) and 285 mμ (ϵ 6500).

(16) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 2854 (1951).

ml. of ether were added simultaneously, dropwise, to 100 ml. of ether while stirring and cooling during 30 min. A white solid separated. After the additions were completed, the mixture was stirred 30 min. longer, and then filtered. The white solid weighed 11.6 g. (90%), m.p. 114–115°. One recrystallization from water gave the analytical sample, m.p. 116–117°; infrared bands at 2.89, 2.98, 5.81, and 5.98 μ.

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.27; H, 6.53; N, 10.05.

N-(2-Aminoethyl)acetoacetamide Hydrobromide (IX).—The benzyloxycarbonyl group was removed from VIII using the method of Ben-Ishai and Berger.[17] A mixture of 27.8 g. (0.1 mole) of VIII and 200 ml. of 30–35% hydrogen bromide–acetic acid solution was allowed to stand at room temperature, with occasional shaking, for 1 hr., at which time the evolution of carbon dioxide had ceased. A large volume of ether was added, and the oil which separated was triturated with fresh portions of ether until it became a nearly white solid. This solid (IX) weighed 25.5 g. (quantitative). It was very hygroscopic and was stored in a vacuum desiccator until used in the next step without further purification.

7-Methyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one (Xa).—A mixture of 9.0 g. (0.04 mole) of IX in 1000 ml. of chloroform was stirred as ammonia was bubbled through the mixture for 1 hr. Sodium sulfate was added, the mixture was filtered, and the filtrate was evaporated. The residue, a yellowish-white solid, wt. 4.7 g., was recrystallized from chloroform to give 1.8 g., m.p. 160–163.5°, of Xa as a white crystalline product. This solid gradually turned yellow on standing several days. The analytical sample was prepared by recrystallization from alcohol–ether, m.p. 163.5–165°. The infrared spectrum showed bands at 2.89, 3.05, 3.37, and 6.14 μ. The ultraviolet spectrum showed an absorption peak at 285 mμ (ε 15,900); addition of acid resulted in no absorption above 220 mμ.

Anal. Calcd. for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21; mol. wt., 126. Found: C, 56.74, 56.92; H, 7.91, 8.11; N, 22.36; mol. wt., 126 (mass spectrometry) and mol. wt., 128 (isothermal distillation).

(17) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

The hydrochloride of Xa was prepared with alcoholic hydrogen chloride, m.p. 165–167° dec. The hydrochloride was hygroscopic.

Anal. Calcd. for $C_6H_{11}ClN_2O \cdot {}^1/_4H_2O$: C, 43.12; H, 6.94; Cl, 21.22; N, 16.76. Found: C, 42.94; H, 6.75; Cl, 21.15; N, 16.75.

The picrate of Xa was prepared in alcohol, m.p. 170.5–171° dec.

Anal. Calcd. for $C_{12}H_{13}N_5O_8$: C, 40.57; H, 3.69; N, 19.71. Found: C, 40.37; H, 3.79; N, 19.62.

Hexahydro-7-methyl-1,4-diazepin-5-one (IVa).—A solution of 5 g. (0.04 mole) of Xa, 100 ml. of ethanol, and 11 ml. (0.04 mole) of 3.9 *N* alcoholic hydrogen chloride was reduced with hydrogen at room temperature and 19 p.s.i. in the presence of 1.0 g. of platinum oxide. Within an hour the theoretical amount of hydrogen was absorbed. The catalyst was removed and the solvent was evaporated. The sticky residue was dissolved in chloroform and treated with ammonia. The mixture was filtered and the filtrate was evaporated. This gave 4.1 g. (80%) of IVa as a white solid. Two recrystallizations from chloroform–petroleum ether and one from ethyl acetate gave 2.9 g. of crystalline material, m.p. 105–108°. The analytical sample was obtained by dissolving a sample in ether, filtering to remove a trace of insoluble material, and evaporating the ether. This raised the m.p. to 109–111°. There was a strong band at 6.00 μ in the infrared spectrum and no absorption in the ultraviolet.

Anal. Calcd. for $C_6H_{12}N_2O$: C, 56.22; H, 9.44; N, 21.86. Found: C, 55.94; H, 9.13; N, 21.76.

The picrate of IVa was prepared in alcohol and recrystallized from water, m.p. 232–233° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O_8$: C, 40.34; H, 4.23; N, 19.60. Found: C, 40.65; H, 4.19; N, 19.95.

Acknowledgment.—We wish to thank Mr. L. M. Brancone and associates for the analytical data and molecular weight determinations by isothermal distillation; Dr. A. Struck and associates for a molecular weight determination by mass spectrometry; and Mr. W. Fulmor and Dr. J. Lancaster and their associates for the determination and interpretation of the n.m.r. data.

Reductions with Ruthenium Catalyst. III. Hydrogenation of Nuclear Substituted Anilines

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A study of the activity of ruthenium dioxide in the hydrogenation of substituted anilines is carried out. The effect of the catalyst on certain potentially hydrogenolyzable groups is reported along with the effect of substituents on reduction.

In the past we had prepared a few substituted cyclohexylamines as intermediates for compounds to be tested as sweetening agents. For the most part they were obtained by reduction of the corresponding anilines with ruthenium dioxide. Our continuing interest in the hydrogenation of nitrogen-containing compounds with this catalyst[1] led us to expand the series to cover a wide range of substituents.

Our purpose was not only to note the effect of substitution on hydrogenation, but also to see the effect of the catalyst on those groups which have a tendency to hydrogenolyze.

Alkyl substituents on the ring do not appear to have too profound an effect on the rate of hydrogenation under the conditions used in this work.

(1) M. Freifelder and G. R. Stone, *J. Am. Chem. Soc.*, **80**, 5278 (1958); M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).