A few years ago the stereoisomeric hydrocarbons Ib were converted *via* their ketones Ic to dibasic acids of known configuration.[4] As a consequence the saturated ketones Ia were transformed into their aromatic counterparts Ic by Wolff-Kishner reduction followed by chromic acid oxidation and the 2,4-dinitrophenylhydrazones of the latter compared with authentic samples.[5] These experiments were in full accord with the previous stereochemical assignment[2,3] of the isomers of Ia.

EXPERIMENTAL

Hydrocarbons Ib. A mixture of 350 mg. of *cis*-Ia and 0.7 ml. of hydrazine hydrate in 12 ml. of diethylene glycol was heated at 190° for 1 hr. After cooling to 70°, a solution of 700 mg. of sodium in 10 ml. of diethylene glycol was added and the mixture heated at 215–220° for 6 hr. Thereupon the mixture was cooled, poured into 100 ml. of saturated brine solution, and extracted with benzene. The extract was washed with water, dried, and its solvent removed, leaving 265 mg. of an oil. Chromatography of the latter on 25 g. of alumina and elution with petroleum ether (b.p. 30–60°) gave 204 mg. of colorless oil, which was used directly in the chromic acid oxidation.

A similar operation on 150 mg. of *trans*-Ia yielded 105 mg. of crude product which on chromatography on 9 g. of alumina led to 88 mg. of colorless hydrocarbon. The latter also was used for oxidation without further purification.

Ketones Ic. A solution of 50 mg. of chromic oxide in 0.1 ml. of water and 0.4 ml. of glacial acetic acid was added dropwise with stirring to a solution of 52 mg. of *cis*-Ib in 0.5 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature for 6.5 hr. and then was diluted with 15 ml. of saturated brine solution and extracted with chloroform. The extract was washed three times with 10% sodium hydroxide solution and once with saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. The resulting 30 mg. of residual neutral oil was chromatographed on 5 g. of alumina, yielding 9 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26 (m)μ, by 9:1 petroleum ether–ether elution.

A similar operation on 126 mg. of *trans*-Ib, however for 11 hr. reaction time,[6] led to 105 mg. of neutral oil which on chromatography on 10 g. of alumina and 9:1 petroleum ether–ether elution gave 31 mg. of colorless liquid ketone, infrared spectrum (chloroform): C=O 5.88(s)μ, C=C 6.26(m)μ.

2,4-Dinitrophenylhydrazones. The derivative of *cis*-Ic melted at 182–183°, m.m.p. 179–183° with authentic sample[4] (m.p. 182.5–184°), identical infrared spectrum with that of an authentic sample.

The derivative of *trans*-Ic melted at 208–210.5°, m.m.p. 207°–210° with an authentic specimen[4] (m.p. 209.5–210.5°), identical infrared spectrum with that of an authentic specimen.

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[4] R. A. Barnes and M. T. Beacham, *J. Am. Chem. Soc.*, **77**, 5388 (1955) and preceding papers.

[5] The authors wish to express their gratitude to Professor Barnes for his gift of comparison samples.

[6] The *trans* hydrocarbon is over-oxidized more slowly than its *cis* isomer [*cf.* E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211 (1958)].

A Reinvestigation of the Action of Formaldehyde on 1,2- and 1,3-Hydroxyamines in the Pyrrolidine and Piperidine Series

Richard K. Hill and Larry J. Loeffler

Received March 21, 1960

In 1913, Hess reported[1] a remarkable synthesis of the coca alkaloid hygrine (V) by heating the amino alcohol I with formaldehyde in acidic solution. Although direct comparison of his product with the natural base was not made at the time, the empirical formula and the close correspondence of the physical and chemical properties of the base and its derivatives[2] all supported his conclusion that a disproportionation reaction had occurred which resulted in simultaneous methylation of the nitrogen and oxidation of the secondary hydroxyl. Continued investigation showed that the reaction was apparently a general one for 1,2- and 1,3-hydroxyamines, and over a dozen examples were reported.[4,5]

It must be noted that except in two cases (those which gave hygrine and the isomeric ketone VI, both of which were reported to yield oximes) no experimental evidence was offered for the presence of either the *N*-methyl or the carbonyl group in the products. The structures were proposed solely on the empirical formulas of their picrates and the analogy to the initial reaction which had afforded hygrine. The only chemical behavior reported was first, that many of the reaction products gave a positive silver mirror test, and second, that with the exception of the two cases already mentioned, every effort to prepare carbonyl derivatives yielded only the corresponding derivative of formaldehyde plus the original hydroxyamine.

It is not surprising, in the face of this tenuous evidence, that it soon became apparent that some of Hess' products were incorrectly formulated. It was pointed out by both Kohn[6] and Rolfes[7] that the products from the reactions of aldehydes with diacetone alcohol amine were more likely tetrahydro 1,3-oxazines. In two other cases,[8,9]

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[1] K. Hess, *Ber.*, **46**, 4104 (1913).

[2] The picrate of the synthetic base was first reported to melt at 174°, although hygrine picrate melts at 149–150°; Hess regarded this discrepancy as due to differences in purity of the two samples. Some years later,[3] he reported that the original sample of the synthetic picrate now melted at 149–150°, and did not depress the melting point of authentic hygrine picrate.

[3] K. Hess and H. Fink, *Ber.*, **53**, 781 (1920).

[4] K. Hess, F. Merck, and C. Uibrig, *Ber.*, **48**, 1886 (1915).

[5] K. Hess and C. Uibrig, *Ber.*, **48**, 1974 (1915).

[6] M. Kohn, *Ber.*, **49**, 250 (1916).

[7] H. Rolfes, *Ber.*, **53**, 2203 (1920).

[8] K. Hess and A. Eichel, *Ber.*, **50**, 1407 (1917).

[9] K. Hess and W. Corleis, *Ber.*, **54**, 3010 (1921).

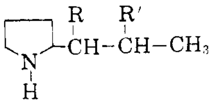
including the closely related piperidine alcohol III, Hess found that the supposed aminoketones were different from genuine samples prepared by other routes, and was forced to assign tetrahydrooxazine and oxazolidine structures to them, too.

While it is surprising that the reaction should take different courses with compounds of such similar structure, there seemed to be no doubt about the constitution of the ketones from I and II, as both reportedly formed oximes of the expected composition. Hess' work is still widely cited in texts as the first synthesis of hygrine. It appeared worthwhile to reinvestigate these reactions to confirm their authenticity and with a view to studying the mechanism.

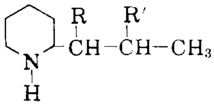
The reaction of the pyrrolidine alcohols I and II with formaldehyde in aqueous acid was carried out in sealed tubes exactly as described by Hess. Basic products were isolated whose empirical formulas and physical properties agreed with those reported. The infrared spectra quickly revealed, however, the complete absence of absorption in the carbonyl region. As the spectra were also devoid of N—H and O—H absorption, the only plausible structures for the products are the tetrahydrooxazine VII and the oxazolidine IX, respectively. A closer examination of the spectra showed the presence of the triplet in the 1080–1200 cm.$^{-1}$ region characteristic of cyclic compounds containing the —N—C—O— grouping.[10] Also consistent with this formulation was the liberation of formaldehyde, identified as its dimedone derivative, on mild hydrolysis with dilute hydrochloric acid. Even when the initial reaction mixture was made alkaline and extracted with ether, no trace of carbonyl absorption could be found in the infrared spectra of the total extracts, and consequently it must be concluded that *N*-methyl aminoketones are not formed in detectable amounts in these reactions.[11] We are unable to account for the reported formation of oximes from these two bases, since in our hands, the reaction of VII with hydroxylamine following Hess' procedure gave no solid product.

We have also carried out the reaction with compounds III and IV, the corresponding alcohols of the piperidine series. The mixture of diastereoisomers of formula III was first reported[4] to yield an *N*-methyl aminoketone, but later[8] the structure was changed to a tetrahydrooxazine and the isolation of a second product containing an additional carbon was claimed. We were able to isolate only the base VIII, with an analysis corresponding to $C_9H_{17}NO$; the tetrahydrooxazine structure is again supported by the infrared spectrum[12] and the hydrolysis to formaldehyde. In this case, the starting amino alcohol was also isolated from the hydrolysis.

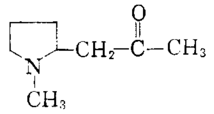
Finally, in the case of *d,l*-conhydrine (IV), the starting material was available as a single isomer of known configuration.[13] Once again, the product from formaldehyde treatment was shown to be the oxazolidine (X) by its infrared spectrum and hydrolysis to formaldehyde.



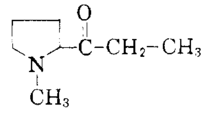
I. R=H, R'=OH
II. R=OH, R'=H



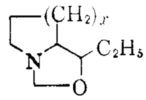
III. R=H, R'=OH
IV. R=OH, R'=H



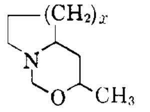
V



VI



IX. $x=1$
X. $x=2$



VII. $x=1$
VIII. $x=2$

EXPERIMENTAL

Preparation of starting amino alcohols. 1-α-Pyrrolidyl-2-propanol (I), prepared by the method of Hess,[14] distilled at 115–125° (16 mm.), lit. b.p. 115–120° (15 mm.).

1-α-Pyrrolidyl-1-propanol (II). 1-α-Pyrryl-1-propanone was prepared by a modification of Oddo's method[15]; steam distillation of the acidified Grignard reaction mixture gave directly the pure ketone, m.p. 52–53°, lit. m.p. 52.5°, in 12–14% yields. Reduction with sodium and ethanol, according to Hess,[14] followed by vacuum sublimation, gave hygroscopic needles of II, m.p. 45–52°, lit. m.p. 50°. The picrate, after three recrystallizations from ethanol, melted at 125–127°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06; N, 15.64: Found: C, 43.41; H, 5.17; N, 15.78.

1-α-Piperidyl-2-propanol (III) was prepared by hydrogenation of 1-α-pyridyl-2-propanol[16] in 85–90% yields. The mixture of stereoisomers obtained melted at 52–59°; reported[17] melting points are 75° and 70–71° for the two pure isomers, 45–55° for the mixture obtained by hydrogenation.

1-α-Piperidyl-1-propanol (*d,l-conhydrine*) (IV), m.p. 99.5–100°, was synthesized as described previously.[13]

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(10) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953).

(11) After this work had been completed, the same conclusion was announced by Lukeš and co-workers; R. Lukeš, J. Kloubek, J. Kovář, and K. Bláha, *Coll. Czech. Chem. Comm.*, **24**, 2433 (1959).

(12) The crude basic product showed weak but reproducible absorption at 5.82 and 5.95 μ, but the grouping responsible for this absorption could not be identified. No pure material containing either band could be isolated, a 2,4-dinitrophenylhydrazone could not be formed from the crude product, and the picrate of the crude base showed no absorption in this region.

(13) R. K. Hill, *J. Am. Chem. Soc.*, **80**, 1609 (1958).

(14) K. Hess, *Ber.*, **46**, 3113 (1913).

(15) B. Oddo, *Ber.*, **43**, 1012 (1910).

(16) L. A. Walter, *Org. Syntheses*, **Coll. Vol. II**, 757.

(17) H. C. Beyerman, J. Eenshuistra, W. Eveleens, and A. Zweistra, *Rec. trav. chim.*, **78**, 43 (1959).

Reaction of I *with formaldehyde.* A solution of 2.0 g. of 1-α-pyrrolidyl-2-propanol in 5 ml. of water was acidified with concd. hydrochloric acid and treated with 6 ml. of 40% formalin solution. The resulting mixture was heated in a sealed pyrex tube at 117° (refluxing 1-butanol) for 4 hr. The dark brown contents of the tubes were cooled, made alkaline with 50% potassium hydroxide solution, and the base extracted with ether and dried over magnesium sulfate. Vacuum distillation gave 1.5 g. of a colorless liquid, b.p. 83–84° (21 mm.), lit.[1] b.p. 89–92° (22 mm.). The picrate melted at 174–175°, lit.[2] m.p. 174°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.33; H, 4.93; N, 15.44.

In an attempt to prepare the reported oxime, 1.4 g. of VII, 0.7 g. of hydroxylamine hydrochloride and 0.6 g. of potassium hydroxide were warmed on the steam bath in 20 ml. of water for 2 hr. Working up the mixture in the manner described by Hess[1] gave no solid products.

Hydrolysis of VII. A solution of 0.25 g. of VII in 5 ml. of ethanol, 5 ml. of 1*N* hydrochloric acid, and 5 ml. of a 10% alcoholic solution of dimedone was refluxed for 2 hr., neutralized with potassium hydroxide and concentrated on the steam bath. Chilling gave a crude solid, which was recrystallized from ethanol to yield 50 mg. of the dimedone derivative of formaldehyde, m.p. and mixed m.p. 188–191.5°.

Reaction of II *with formaldehyde.* The base (1.66 g.) isolated by vacuum distillation of the product from reaction of 2.0 g. of II with formaldehyde, as described above, gave a picrate, needles from ethanol, melting at 101–103°, lit.[1] m.p. 103°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.15. Found: C, 45.35; H, 5.03; N, 15.38.

Hydrolysis of the base in the presence of dimedone, as described above, gave the crystalline derivative of formaldehyde.

Reaction of III *with formaldehyde.* A solution of 10 g. of III in 17.5 ml. of water was acidified with 8.2 ml. of concd. hydrochloric acid, treated with 10.5 ml. of 40% formalin solution, and heated at 117° for 4 hr. The mixture was worked up as described above, affording 9.1 g. of colorless liquid, b.p. 110–113° (14 mm.), 70–72° (6 mm.), lit.[3] b.p. 108–111° (28 mm.).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.70; H, 11.04; N, 9.03. Found: C, 69.31; H, 11.06; N, 9.08.

The picrate, twice recrystallized from ethanol, melted at 140.5–144°, lit. m.p. 162–163°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.24; N, 14.58. Found: C, 46.89; H, 5.31; N, 14.71.

Hydrolysis of the base in the presence of dimedone again afforded the dimedone derivative of formaldehyde. The starting amino alcohol (III) was also recovered by crystallization and identified by its infrared spectrum.

Reaction of IV *with formaldehyde.* The reaction of 1.70 g. of IV with formaldehyde was carried out as described above, and yielded 1.50 g. of colorless product. The picrate was recrystallized twice from ethanol, and melted at 142–144°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: 46.87: H, 5.24; N, 14.58. Found: C, 47.06; H, 5.11; N, 14.85.

Formaldehyde was isolated as the dimedone derivative when the base was hydrolyzed as described above.

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The Dinitration of *m*-Toluic Acid

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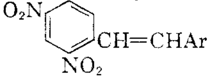
Received February 29, 1960

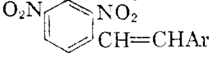
The first report of the dinitration of *m*-toluic acid is that of van Scherpenzeel[1a] who nitrated the acid in one- to two-gram quantities with 100% nitric acid and obtained in an unspecified, low yield a dinitro acid (m.p. 173°) which he formulated as 2,6-dinitro-*m*-toluic acid.[1b] From methyl *m*-toluate by the same procedure he obtained, again in an unspecified, low yield, a methyl ester (m.p. 104°) which he considered to be methyl 2,6-dinitro-*m*-toluate because it could be hydrolyzed with hydrochloric acid to the dinitro-*m*-toluic acid he had already prepared. No direct comparison was made of the two samples of the dinitro acid and no comment was made about the ready hydrolysis of a di-*ortho* substituted benzoic ester.

In the second report of the dinitration of *m*-toluic acid, Hargreaves and McGookin[2] described the use of mixed acid to furnish in 60% yield a dinitro-*m*-toluic acid which they considered to be identical with the acid obtained by van Scherpenzeel. They converted the acid to the acid chloride with thionyl chloride. From the crude acid chloride with methanol they obtained a methyl ester, m.p. 104°, which confirms the identity of their acid and van Scherpenzeel's, and a second unidentified product, m.p. 67°, which casts doubt on the homogeneity of their acid.

Since the nitration of *m*-toluic acid with 100% nitric acid was so unpromising and inconvenient, we used mixed acid and obtained consistent yields of 85% of a crude product which is a mixture containing 2,6-dinitro- and 4,6-dinitro-*m*-toluic acid in approximately equal amounts. The two acids can be separated and structures may be assigned to them from the behavior of the crude product on heating with methanol containing sulfuric acid: 4,6-dinitro-*m*-toluic acid is converted to the methyl ester (m.p. 104°) while 2,6-dinitro-*m*-toluic acid is unaffected. The two reactions, nitration and treatment with methanol and sulfuric acid, show that the earlier workers actually had in hand an impure 4,6-dinitro-*m*-toluic acid rather than the 2,6-dinitro acid as they believed. It also follows from these two experiments that 2,6-dinitro-*m*-toluic acid and its esters have not hitherto been prepared, that the description of these compounds in the literature are erroneous, and that the substituted stilbenes prepared by Hargreaves and McGookin[2] from aromatic aldehydes and the 104° methyl ester have structure I rather than the structure II that was assigned to them.



I



II

(1a) L. van Scherpenzeel, *Rec. trav. chim.*, **20**, 149–182 (1901).

(1b) In *m*-toluic acid and its substitution products the carboxyl group and the methyl group are assigned positions 1 and 3, respectively.

(2) K. R. Hargreaves and A. McGookin, *J. Soc. Chem. Ind. (London)*, **69**, 190 (1950).