tone–ethanol), lit.[5] m.p. 232–233°; and epimer B, 1.0 g., m.p. 71–72°, lit.[5] m.p. 72°, picrate[36] m.p. 174–176° (95% ethanol), hydrobromide m.p. 242–244° (acetone), lit.[5] m.p. 243–244°. Unexpectedly, epimer B was the first eluted from the alumina column in this series. A mixed middle fraction was also obtained.

The 3-hydroxyquinolizidines were isolated by distillation. Thus, 8.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol was completely reduced in 1.5 hr. over 2.0 g. of 5% ruthenium on carbon (Engelhard Industries, Inc.) at 70 p.s.i.g. and 28° in a Parr hydrogenation apparatus. The catalyst was filtered off and the solvent was removed under reduced pressure to give a 76:24 A–B ratio (g.l.c. analysis). Distillation gave fraction 1, 4.0 g. (>98% A), b.p. 51° (0.25 mm.), $n^{28}D$ 1.4930; and fraction 2, 2.8 g. (65% A), b.p. 51–72° (0.25 mm.). Fraction 1 solidified in the freezer to give epimer A, m.p. 23–25°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; O, 10.31; equiv. wt., 155.2. Found: C, 69.8; H, 11.0; O, 10.6; equiv. wt., 156.

The picrate of A was prepared in ether and gave m.p. 115–117°. Attempts to recrystallize this picrate led to material which melted lower and over a wider range. The hydrobromide gave m.p. 206–208° (acetone).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.7; H, 7.7.

3-Hydroxyquinolizidine, epimer B, was obtained by reduction of 5.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol over 1.0 g. of 10% palladium-on-carbon catalyst (A. D. Mackay and Co.) at 70 p.s.i.g. of hydrogen and 25°. Reduction was completed in 1 hr. The catalyst was filtered off, and the solvent was removed under reduced pressure to give a 3:97 A–B product ratio (g.l.c. analysis). Distillation (78–81°, 0.25 mm.) gave fraction 1, 0.4 g. (94% B); fraction 2, 1.2 g. (97% B); and fraction 3, 2.6 g. (99% B). On standing in the freezer, fraction 3 crystallized to give epimer B, m.p. 59–62°, which upon recrystallization from petroleum ether melted at 65–66°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; equiv. wt., 155.2. Found: C, 69.6; H, 11.0; N, 9.1; equiv. wt., 153.

The hydrobromide of B gave m.p. 239–240.5° (acetone–methanol, 2:1).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.5; H, 7.8.

The picrate of B gave m.p. 161.5–162° upon precipitation from ether.[38]

Acknowledgment.—Some of the infrared spectral data were obtained by Mr. R. Piffath; the elemental analyses were carried out by the Microanalytical Laboratory of the Chemical Research Division of these laboratories.

(36) Picrate m.p. 174–175°[37] and 175.5–176.5°[4] have been obtained from products now known[7] to have been about 84:16 B–A.

(37) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 443 (1955).

(38) A picrate, m.p. 161.5–162.5°, has been obtained[4,37] by recrystallization of the product from a mixture now known[7] to have been about 85:15 B–A.

Azabicyclic Alcohols. II. Chemical and Catalytic Reduction of the Ketoquinolizidines[1]

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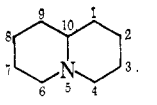
Catalytic hydrogenations of 1-, 2-, and 3-ketoquinolizidine have been studied on platinum oxide, rhodium, ruthenium, and palladium. Epimeric racemates of the corresponding hydroxyquinolizidines have been obtained in proportions which vary with the nature of the catalyst and acidity of the reducing medium. On platinum oxide and rhodium some hydrogenolysis of the carbon–oxygen bond occurs. The unprotonated bridgehead nitrogen atom appears to influence the stereochemistry of the hydrogenations by virtue of its ability to bond with the surface and thus produce an "anchor effect." Alkali metal–ethanol and metal hydride reductions of these ketones give a predominance of the equatorial hydroxyl epimer in all cases.

The addition of hydrogen to a cyclic ketone is capable of providing a convenient method of stereoselective synthesis. It also provides a direct insight into the stereochemistry and mechanism governing the attack of the carbonyl group by various reducing agents. The structural elucidation of the 1-, 2-, and 3-hydroxyquinolizidine racemates (1)[2] has permitted a systematic stereochemical study of the chemical and catalytic reduction of the corresponding ketones.

The general theory of the stereochemistry of catalytic hydrogenation has been summarized by Burwell.[3] In an extended series of investigations,[4] each of the four possible decalone racemates has been reduced catalytically on platinum and by chemical methods. The stereochemical data for the chemical reduction



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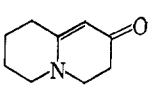

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of various substituted cyclohexanones has recently been reviewed.[5]

The basic purpose of this research was to determine the extent by which the stereoselectivity of the addition of hydrogen to an azabicyclic ketone would vary as a function of substrate, reducing agent, catalyst, conditions, *etc.* In several previous investigations of this general type, appreciable confusion has arisen in the determination of the relative amounts of stereoisomers resulting from the reduction *per se*. The recent development of gas–liquid chromatography (g.l.c.) has provided a most convenient and reliable method for the analysis of reduction mixtures.[6]

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

(3) R. L. Burwell, *Chem. Rev.*, **57**, 895 (1957).

(4) (a) W. Hückel, *Nachr. Ges. Wiss. Göttingen Jahresber. Geschaftsjahr Math physik Kl. Fachgruppen: I*, 43 (1923); (b) W. Hückel, *Ann.*, **441**, 1 (1925); (c) W. Hückel, *ibid.*, **451**, 109 (1927); (d) W. Hückel, *ibid.*, **533**, 1 (1938); (e) W. Hückel and G. Stelzer, *Chem. Ber.*, **88**, 984 (1955); (f) W. Hückel, D. Maucher, O. Fechtig, J. Kurz, M. Heinzel, and A. Hubele, *Ann.*, **645**, 115 (1961).

(5) A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962).

(6) S. Siegel and B. Dmuchovsky, *J. Am. Chem. Soc.*, **84**, 3132 (1962); W. G. Dauben and R. E. Bozak, *J. Org. Chem.*, **24**, 1596 (1959); H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *ibid.*, **28**, 2407 (1963).

TABLE I

COMPOSITION OF MIXTURES RESULTING FROM CATALYTIC HYDROGENATIONS OF KETOQUINOLIZIDINES

Quinolizidine hydrogenated	Catalyst	Medium	Products, %[a] Racemate A	Racemate B	Quinolizidine	Hydrogenation, %
1-Keto	PtO_2	EtOH	33	67	0	100
1-Keto	PtO_2	Aqueous HCl	55	40	5	100
1-Keto	5% Rh–C	EtOH	26	74	0	100
1-Keto	5% Rh–C	Aqueous HCl	43	57	0	100
1-Keto	5% Ru–C	EtOH	71	29	0	100
1-Keto	5% Ru–C	Aqueous HCl	81	19	0	20–75
1-Keto	10% Pd–C	EtOH	7	93	0	100
1-Keto	10% Pd–C	Aqueous HCl	68	32	0	47
2-Keto	PtO_2	EtOH	26	74	0	98
2-Keto	PtO_2	Aqueous HCl	3	78	19	100
2-Keto	5% Rh–C	EtOH	15	85	0	100
2-Keto	5% Rh–C	Aqueous HCl	36	62	2	100
2-Keto	5% Ru–C	EtOH	40	60	0	100
2-Keto	5% Ru–C	Aqueous HCl	33	67	0	100
2-Keto	10% Pd–C	EtOH	5	95	0	20
2-Keto	10% Pd–C	Aqueous HCl	26	74	0	10–65
3-Keto	PtO_2	EtOH	29	71	0	100
3-Keto	PtO_2	Aqueous HCl	33	33	34	100
3-Keto	5% Rh–C	EtOH	19	81	0	100
3-Keto	5% Rh–C	Aqueous HCl	73	6	21	100
3-Keto	5% Ru–C	EtOH	72	28	0	100
3-Keto	5% Ru–C	Aqueous HCl	86	14	0	83–100
3-Keto	10% Pd–C	EtOH	3	97	0	100
3-Keto	10% Pd–C	Aqueous HCl	82	18	0	32–90
$\Delta^{1,10}$-2-Keto	PtO_2	EtOH	29	67	4	100
$\Delta^{1,10}$-2-Keto	PtO_2	Aqueous HCl	2	98	0	100
$\Delta^{1,10}$-2-Keto	5% Ru–C	EtOH	13	87	0	100

[a] See ref. 2 for structural assignments of the hydroxyquinolizidines.

Results

Table I summarizes the products obtained from the catalytic hydrogenations of 1-, 2-, and 3-ketoquinolizidine in both ethanol and aqueous HCl. In the 1- and 3-hydroxyquinolizidines, racemate A has the *cis*-1,10- and *cis*-3,10-hydrogen configurations, respectively; racemate B of the 2-hydroxyquinolizidines has the *cis*-2,10-hydrogen configuration. In each case, the A and B racemates are axial and equatorial alcohols, respectively. Preparative scale reductions using smaller catalyst–substrate ratios gave A–B ratios in reasonable accord with the results listed in Table I. For example, the hydrogenation of 3-ketoquinolizidine on 5% ruthenium on carbon in ethanol gave an A–B ratio of 76:24 and on 10% palladium on carbon in ethanol a ratio of 3:97. The hydrogenation of $\Delta^{1,10}$-2-ketoquinolizidine (II) gave only the 2-hydroxyquinolizidine racemates and quinolizidine as products.

For the acidic hydrogenations, no distinct correlation of racemate ratios appears to exist as one proceeds from catalyst to catalyst with each of the three ketones. The ethanolic hydrogenations, however, clearly reveal that on the four catalysts the percentage of the axial hydroxyl epimer always decreases in the order Ru > PtO_2 > Rh > Pd. On each of the four catalysts in ethanol, the hydrogenations of 1- and 3-ketoquinolizidine give results which are quite similar quantitatively.

Since it is known that cyclic alcohols may undergo epimerization on a metal catalyst,[7] attempts were made to isomerize a mixture of the 2-hydroxyquinolizidines (A–B = 47:53) over each of the metal catalysts used in this study. Isomerizations were tried in both ethanol and aqueous HCl (pH 1–2) using the same procedures and methods of work-up as were used in the ketone hydrogenations. In all cases, the composition of the 2-hydroxyquinolizidine mixture remained the same within experimental error. It may thus be concluded that once the amino alcohol has been desorbed from the active surface, it cannot undergo subsequent isomerization. Hence, the relative amounts of amino alcohols obtained from the ketoquinolizidine hydrogenations are the result of the original reduction process on the catalyst.

The relative amounts of hydroxyquinolizidine racemates resulting from chemical reductions of the corresponding ketones are given in Table II. With each ketone, the relative proportions of amino alcohol

TABLE II

COMPOSITION OF MIXTURES RESULTING FROM CHEMICAL REDUCTIONS OF KETOQUINOLIZIDINES

Quinolizidine reduced	Reducing agent	% racemate, A–B[a]
1-Keto	Na, EtOH	18:72
1-Keto	K, EtOH	17:83
1-Keto	$LiAlH_4$	16:84
1-Keto	$NaBH_4$	17:83
2-Keto	Na, EtOH	10:87
2-Keto	K, EtOH	4:90
2-Keto	$LiAlH_4$	11:89
2-Keto	$NaBH_4$	10:90
3-Keto	Na, EtOH	16:81
3-Keto	K, EtOH	19:69
3-Keto	$LiAlH_4$	16:84
3-Keto	$NaBH_4$	12:88

[a] See ref. 2 for structural assignments of racemates. In those reductions in which the sum of A and B does not equal 100, the remainder of the products consisted of minor g.l.c. peaks which were not identified.

(7) R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

racemates resulting from all of the chemical reducing agents are very similar, with the equatorial epimer always predominating.

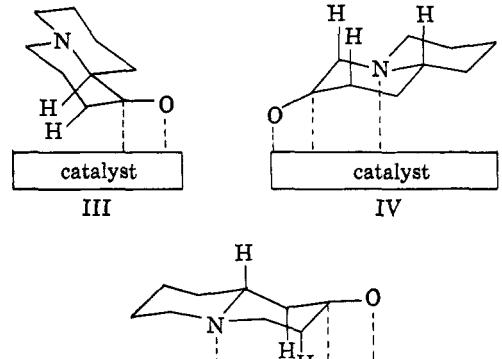
Discussion

Catalytic Hydrogenations.—The great variation of racemate ratios resulting from the ketoquinolizidine hydrogenations clearly reveals the extent to which the stereochemistry of a given catalytic hydrogenation can vary as a function of catalyst and medium. Any explanation of these stereochemical results should be based upon the influence which solvent and catalyst can exert upon the different modes of adsorption of the carbonyl group on the active spots of the catalyst. With the practical catalysts used in this work, the nature and structure of these active spots is presently so poorly understood[8] that any valid interpretation of the experimental data must be related to the structure of the substrate rather than that of the active catalyst. It is logical to assume[9] that the carbonyl group will preferentially be adsorbed so as to minimize the steric interaction between the surface and the remainder of the molecule. The hydrogen will then be added from the catalyst side of the functional group.[10] The relative amounts of amino alcohol racemates thus obtained from the catalytic hydrogenations should be determined by the relative ease of the two modes of adsorption of the carbonyl group on the active surface. Since all of these hydrogenations were carried out at room temperature, it is reasonable to conclude that the hydrogenations are proceeding through the keto rather than the encl form.[11]

The preceding paper in this series[2] has discussed the stereochemistry of the quinolizidine ring system. Due to the possibility of an equilibrium between *cis* and *trans* ring fusions, any attempt to correlate the stereochemistry of the ketoquinolizidine hydrogenations with the various possible conformations of the respective ketones is, at best, difficult. If it may be assumed that each of the three ketones is preferentially adsorbed as a *trans* ring-fusion conformer,[12] one is led to some interesting conclusions. The increased amount of the axial hydroxyl epimer as one proceeds from Pd to Rh to PtO_2 to Ru in each set of ethanolic hydrogenations indicates that the ease of equatorial addition of hydrogen increases in the same order. This, in turn, should reflect the ease, relative to other possible conformers, with which the *all-chair trans* ring-fusion conformer is adsorbed on the catalyst surfaces within this series. III depicts the preferred mode of adsorption of the all-chair *trans* ring-fusion conformer of 1-ketoquinolizidine. Thus for each ketone the ease of adsorption of this conformer in ethanol appears to decrease in the order, Ru > PtO_2 > Rh > Pd.

The hydrogenations of 1- and 3-ketoquinolizidine reveal that on each catalyst the proportion of the equatorial hydroxyl epimer is increased when the solvent is changed from aqueous HCl to ethanol. Assuming again a *trans* ring fusion, it is seen that the presence of the unshared pair of electrons on the bridgehead nitrogen appears to induce more addition of hydrogen from their side of the ring system. This leads to the postulation that the nitrogen may be forming a dative bond with the surface, thus producing an "anchor effect" which will favor the addition of hydrogen from the side opposite the C-10 bridgehead hydrogen. The operation of the anchor effect in 3-ketoquinolizidine is depicted by IV. The extent to which the anchor effect will influence the stereochemistry of the hydrogenation should be determined by the availability of a catalyst site at an appropriate distance (approximately 2.4 Å.) from the site activating the carbonyl carbon. It is well known that, in general, compounds with an unshared pair of electrons on nitrogen are more readily hydrogenated in acid than in basic solution. This may be ascribed to the ability of the unshared nitrogen electrons to bond with the active surface and thus poison it.[13] The amino nitrogen has been shown[14] to be capable of catalyst poisoning only when it has an unshared pair of electrons and is thus "unshielded."

For 2-ketoquinolizidine, the anchor effect (V) predicts an increasing amount of the axial hydroxyl epimer as one proceeds from the protonated to the free amino ketone. This prediction is followed on platinum oxide



and ruthenium but not on palladium and rhodium. The explanation for the apparently anomalous behavior on the last two catalysts could lie in the fact that in 2-ketoquinolizidine the carbonyl group is farthest from the nitrogen, and the operation of the anchor effect which requires the simultaneous adsorption of both functional moieties must overcome the steric hindrance imposed by the axial hydrogens at C-1 and C-3 (V).

(8) G. C. Bond, "Catalysis by Metals," Academic Press, New York N. Y., 1962, Chapter 3.

(9) S. Siegel, *J. Am. Chem. Soc.*, **75**, 1317 (1953).

(10) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942). An alternative mechanism for the hydrogenation of ketones [J. H. Brewster, *ibid.*, **76**, 6361 (1954)], which proposes the addition of a hydride ion from the catalyst and a proton from the solvent, is less compatible with the wealth of existing catalytic and physicochemical knowledge concerning hydrogenation than is that of a mechanism involving chemisorption of the carbonyl group and addition of both hydrogens from the catalyst.

(11) Ref. 8, p. 335; L. C. Anderson and N. W. MacNaughton, *J. Am. Chem. Soc.*, **64**, 1456 (1942).

(12) The *trans* ring fusion has been shown to be greatly preferred by the 1-, 2-, and 3-methyl- and 1-, 2-, and 3-hydroxyquinolizidines (*cf.* preceding paper in this series and references contained therein). Analogy with the well-known decalin ring system also predicts a prevalence of the *trans* ring fusion in the ketoquinolizidines. The recent report of S. F. Mason, K. Schofield, and R. J. Wells, [*Proc. Chem. Soc.*, 337 (1963)] tends to confirm this assumption.

(13) In the case of platinum oxide, the decreased activity in nonacidic media has been ascribed to the presence of small amounts of alkali in the catalyst; see, C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.*, **76**, 229 (1954). This, however, should not impair the ability of the free amino nitrogen to bond with the active catalyst surface.

(14) E. B. Maxted, "Advances in Catalysis," Vol. III, Academic Press, New York, N. Y., 1951, p. 136.

This type of hindrance does not occur in the adsorption of 1- and 3-ketoquinolizidine since there will be no axial hydrogens between the carbonyl group and the bridgehead nitrogen on the catalyst side of the ring system. As indicated above, the all-chair *trans* ring-fusion conformer appears to be less readily adsorbed on palladium and rhodium than on platinum oxide and ruthenium. The relative ease of adsorption of this conformer, therefore, should reflect the susceptibility of the catalyst surface toward steric hindrance offered by axial hydrogens.

The small but appreciable quantity of quinolizidine resulting from the hydrogenations on PtO_2 in acid agrees with evaporated film studies[15] which have shown platinum to be the most active transition metal in ketone hydrogenolysis. It is interesting that no hydrogenolysis was observed for the reductions of the saturated ketones on PtO_2 in ethanol.

The hydrogenations of $\Delta^{1,10}$-2-ketoquinolizidine (II) on platinum suggest that the α,β-unsaturated ketone is first reduced at the carbon–carbon double bond, desorbed from the catalyst, readsorbed, and then reduced at the carbonyl group. Corroboration for this comes from recent work[16] which has revealed the analogous $\Delta^{1,9}$-octalone-2 to be hydrogenated on platinum oxide to a mixture of the 2-decalones. On ruthenium, however, it appears that most of the hydrogen is added to II during one period of adsorption on the catalyst, since all-*cis* addition will give the equatorial hydroxyl epimer. These results demonstrate that the assumption of all-*cis* catalytic addition of hydrogen to polyunsaturated compounds should be used with care.

Chemical Reductions.—The alkali metal–alcohol reductions all follow Barton's rule[17] in that the more stable equatorial epimer is the principal product. Such reductions of cyclic ketones are generally conceded to give an equilibrium mixture of epimeric alcohols provided the reduction conditions, especially temperature,[18] are properly maintained. Thus the alkali metal–ethanol reductions of the ketoquinolizidines are subject to thermodynamic control.

The results of this study parallel those of sodium–ethanol and sodium–2-butanol reductions of tropinone[19] which were found to give epimeric ratios of tropine and pseudotropine closely approximating that of the equilibrium composition. It should be pointed out that the epimeric mixtures obtained from the ketoquinolizidine reductions do not reflect the relative stability of the amino alcohols themselves but rather that of their alkoxide ions in equilibrium with a large excess of ethoxide ion in benzene–ethanol solution. Equilibrations of the *cis*-2-decalols in decalin have shown[20] the equilibrium ratio of the alcohols to be significantly different from that of the corresponding alkoxides. The same may well be true for the hydroxyquinolizidines.

(15) C. T. H. Stoddard and C. Kemball, *J. Colloid Sci.*, **11**, 532 (1956); C. Kemball and C. T. H. Stoddard, *Proc. Roy. Soc.* (London), **A246**, 521 (1958).

(16) R. L. Augustine, *J. Org. Chem.*, **28**, 152 (1963). In our work, no attempt was made to stop the hydrogenation at the dihydro stage and identify a reduction intermediate.

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(18) K. D. Hardy and R. H. Wicker, *J. Am. Chem. Soc.*, **80**, 640 (1958).

(19) A. H. Beckett, H. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(20) O. R. Rodig and L. C. Ellis, *J. Org. Chem.*, **26**, 2197 (1961).

The exact nature of the species by which hydrogen is added to the carbonyl carbon in alkali metal–alcohol reductions is unknown. Hückel[21] has suggested that the electrons are first added to the carbonyl group followed by the addition of hydrogen as protons. Whatever the nature of the species, it must be reasonably small in size since, as the ketoquinolizidines and other cyclic ketones have shown, these reductions have very little susceptibility to steric crowding around the trigonal carbon.

The rather close correspondence between the stereochemical results of the alkali metal–ethanol and the metal hydride reductions suggests that the latter may also be directed by thermodynamic control. Such, however, is not the case. It has been shown that epimeric mixtures of tropine–pseudotropine[19] and the 2-methylcyclopentanols[22] are not isomerized under actual reduction conditions. The metal hydride reductions of the ketoquinolizidines thus are apparently not directed by true thermodynamic control. These reductions are subject to product development control[23] since the relative stability of the epimeric alcohols appears to dictate the ratio in which they are obtained. This control is due to the relative stability of the transition states leading to the two epimers paralleling that of the epimers themselves. This indicates that the energy maximum lies at a position on the reaction coordinate such that the transition state partakes of much of the character of the product.

Since product development control will govern the stereochemistry of metal hydride reductions only in the absence of appreciable crowding around the carbonyl carbon, it may be concluded that the approach of the incipient hydride ion to this carbon of the ketoquinolizidines is relatively unhindered. A further conclusion is that the size of the species attacking the carbonyl group is of no consequence in determining the stereochemistry of the ketoquinolizidine reductions.

Experimental

Ketoquinolizidines.—The syntheses of 1-, 2-, and 3-ketoquinolizidine were the same as previously reported.[2] The amino ketones were isolated by vacuum distillation in purity greater than 99.5% as shown by gas–liquid chromatographic analysis. Since these compounds deteriorate and darken upon exposure to air, they were stored in 5-ml. serum bottles under nitrogen at −10°. The serum bottles were fitted with rubber caps through which samples could be drawn with a syringe. $\Delta^{1,10}$-2-Ketoquinolizidine was prepared according to the published procedure.[24] The amino ketone (m.p. 80–81°) was recrystallized from ether and gave an ultraviolet spectrum which coincided with that of the previous report.

Hydrogenation Catalysts.—Commercial catalysts were used in all catalytic hydrogenations. Platinum oxide catalyst was obtained from J. Bishop and Co. Platinum Works, Malvern, Pa. The 10% palladium-on-carbon catalyst was procured from A. D. Mackay, Inc., New York, N. Y., whereas, the 5% ruthenium-on-carbon and the 5% rhodium-on-carbon catalysts were supplied by Englehard Industries, Newark, N. J. All catalysts were stored in tightly closed bottles and used as received.

Catalytic Hydrogenations in Ethanol.—In 5.0 ml. of absolute ethanol was dissolved 0.12–0.15 ml. of the desired ketone.

(21) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Ann.*, **616**, 58 (1958).

(22) J. B. Umland and M. I. Jefriam, *J. Am. Chem. Soc.*, **78**, 2788 (1956).

(23) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(24) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94**, 1774 (1961).

The catalyst (50–100 mg.) was added and the reduction was carried out in a Parr low-pressure hydrogenation apparatus, the total volume of which had been reduced to 545 ml. All hydrogenations were carried out for 30–120 min. at room temperature and 50–60 p.s.i.g. hydrogen pressure. Samples of the filtered reduction mixture were evaporated under a stream of nitrogen to approximately one-tenth their original volume and analyzed by gas–liquid chromatography.

Catalytic Hydrogenations in Aqueous HCl.—The catalyst (50–100 mg.) was added to a solution of the ketone (0.12–0.15 ml.) in 5 ml. of 0.2 *N* hydrochloric acid giving a pH of 1–2. The hydrogenation was carried out using the apparatus and conditions described for the ethanolic hydrogenations. Dilute sodium hydroxide (10%) was added to the filtered reduction mixture until the pH rose to 13. The alkaline solution was extracted with four 10-ml. aliquots of chloroform. From the combined chloroform aliquots approximately 90% of the solvent was removed by distillation through a small Vigreux column. The remaining solution was then concentrated with a stream of nitrogen and analyzed by gas–liquid chromatography.

Alkali Metal–Ethanol Reductions.—In 3 ml. of anhydrous reagent grade benzene was placed the metal (0.6 g. of sodium or 0.9 g. of potassium). To this was added dropwise a solution of 0.12–0.15 ml. of the ketone in 2.0 ml. absolute ethanol. After 2 hr. of reflux, distilled water (5 ml.) was added to the mixture. The aqueous phase was extracted with two 5-ml. aliquots of benzene to quantitatively remove the amino alcohols. The benzene aliquots were combined, concentrated, and analyzed by gas–liquid chromatography.

Sodium Borohydride Reductions.—The ketone (0.12–0.15 ml.) was added dropwise to a solution of sodium borohydride (0.10 g.) in distilled water (5.0 ml.). The mixture was permitted to stand overnight. Concentrated ammonium hydroxide (1.0 ml.) was added and the mixture was allowed to stand for an additional 1–2 hr. The solution was saturated with sodium chloride and extracted with five 10-ml. aliquots of benzene to remove quantitatively the mixture of amino alcohols. The benzene aliquots were combined, concentrated, and then analyzed by g.l.c.

Lithium Aluminum Hydride Reductions.—To 0.10 g. of lithium aluminum hydride in 5.0 ml. of anhydrous ether in an ice bath was added dropwise 0.12–0.15 ml. of ketone; the mixture was warmed to room temperature. Thirty minutes later 0.25 ml. of distilled water was added followed by 0.20 ml. of sodium hydroxide (10%). After standing overnight, the ethereal solution was decanted, filtered, and then analyzed by g.l.c.

Gas–Liquid Chromatographic Analysis.—All g.l.c. analyses were carried out with a 10 ft. × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support.[2] Column temperatures of 208–212° and helium flow rates of 120–150 ml./min. were used. Symmetrical peaks were obtained with a minimum of tailing. Peaks corresponding to the epimeric racemates, parent ketone, and quinolizidine were identified by infrared and g.l.c. comparison with known samples of each. In the catalytic and metal hydride reductions, no other products resulted. Preparative scale catalytic reductions gave yields which were essentially quantitative. Some of the alkali metal–alcohol reductions gave small but appreciable proportions (3–12%) of foreign products which were not identified.

Quantitative determinations of the relative amounts of amino alcohols were made by measuring their relative peak areas on the gas–liquid chromatograms. These measurements were normally made with a disk integrator. Check measurements made by cutting out the peaks and weighing them on an analytical balance or by taking the product of the peak height (h) times the peak width at $h/2$ gave results which were identical with those of the disk integrator within 2%. The detector response of the Aerograph A-90-P apparatus used for all analyses was shown to be the same for racemates A and B of each set of amino alcohols. This was accomplished by analyzing mixtures containing known amounts of pure A and pure B.

In order to demonstrate that the work-up procedures used for the various reductions did not alter the relative amounts of racemates resulting from the reductions themselves, mixtures containing known amounts of quinolizidine and each of the 3-hydroxyquinolizidines were subjected to each of the work-up procedures and then analyzed by g.l.c. In all cases the relative amounts of the constituents were not altered by the work-up to an extent greater than 2%. Since the ratio of 3-hydroxyquinolizidines is more susceptible to alteration during work-up than either of the other sets of amino alcohol racemates,[25] it may be concluded that the methods of work-up of the other reduction mixtures have not altered the epimeric ratios by any significant amount.

The A–B racemate ratios from the various chemical and catalytic reductions were found to be reproducible within ±3%, which is the approximate limit of the error resulting from the work-up procedures and the g.l.c. analyses. This is the same limit of experimental error as has resulted[19] from infrared analyses of tropine–pseudotropine reduction mixtures.

(25) Preliminary experiments using a different work-up procedure revealed the difference in volatility to be the greatest potential source of A–B alteration during the work-ups. This difference is greatest for the 3-hydroxyquinolizidines.

Michael Additions of Nitroform. III. The C_9 Precursor, Potassium Methyl 4,4-Dinitro-2-hydroxybutyrate

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From the examination of the changes in the ultraviolet spectra with time of the nitroform–methyl acrylate system and methyl 4,4,4-trinitrobutyrate decomposition in aqueous dioxane (pH ≃5), it was shown that potassium methyl 4,4-dinitro-2-hydroxybutyrate is the precursor of dimethyl 4,4-dinitro-2-hydroxypimelate (C_9). The only path for the formation of potassium methyl 4,4-dinitro-2-butenoate was found to be the elimination of the elements of nitrous acid from methyl 4,4,4-trinitrobutyrate. The isolation and characterization of potassium methyl 4,4-dinitro-2-hydroxybutyrate and the potassium salt of 5,5-dinitro-3-hydroxypentan-2-one, the methyl vinyl ketone analog, are described. With acrylonitrile as the augend, spectral evidence for the presence in solution of the potassium salt of 3,3-dinitropropionaldehyde was obtained.

The addition of nitroform (pK ≈0)[1] to methyl acrylate in moderately to strongly acidic aqueous solutions was found to give excellent yields of methyl 4,4,4-trinitrobutyrate (MeTNB). The first evidence of competing side reactions was found in a study of the effect of pH upon the yield of MeTNB.[2] In a methanol–water system at pH 1 to ≈3.5, the yield of MeTNB varied between 80 and 90%. On increasing the pH to ≈4.2, the yield of MeTNB fell sharply to 65%. Another sharp decrease in yield occurred on increasing the pH to ≈5, where the yield of MeTNB obtained was only 21%. Under the low yield conditions, it was not possible to recover substantial quantities of unreacted nitroform. This indicated that the low yields were not caused by a pH-dependent equilibrium reaction.

(1) S. S. Novikov, V. I. Slovetski, S. A. Shevelev, and A. A. Fainzil'berg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 598 (1956).

(2) Private communication, M. E. Hill of these laboratories.