TABLE I
TRANSFER HYDROGENATION OF UNSATURATED STEROIDS

Acceptor	Donor	Product	Conversion, %
17β-Hydroxy-5α-androst-1-en-3-one (I)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one	100
17β-Hydroxy-5α-androst-1-en-3-one (I)	Cyclohexanol	17β-Hydroxy-5α-androstan-3-one	5
17β-Hydroxy-5α-androst-1-en-3-one (I)	3-Pentanol	17β-Hydroxy-5α-androstan-3-one	5
17β-Hydroxy-5α-androst-1-en-3-one (I)	1-Butanol	No reduction	
17β-Hydroxy-5α-androst-1-en-3-one (I)	Allyl alcohol	No reduction	
17β-Hydroxy-4-androsten-3-one (II)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one and	5
		17β-Hydroxy-5β-androstan-3-one	20
17α-Pregn-5-en-20-yne-3β,17-diol (III)	Benzyl alcohol	17α-Pregn-5-ene-3β,17-diol	100
3β-Hydroxy-5,16-pregnadien-20-one (IV)	Benzyl alcohol	3β-Hydroxypregn-5-en-20-one	100
3β-Hydroxy-16-methyl-5,16-pregnadien-20-one (V)	Benzyl alcohol	No reduction	
17β-Hydroxy-1,4-androstadien-3-one (VI)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one,	3
		17β-Hydroxy-5β-androstan-3-one,	25
		and 17β-Hydroxy-4-androsten-3-one	72
17β-Hydroxy-4,6-androstadien-3-one (VII)	Benzyl alcohol	17β-Hydroxy-5α-androstan-3-one,	3
		17β-Hydroxy-5β-androstan-3-one,	15
		and 17β-Hydroxy-4-androsten-3-one	82

proved to be by far more effective as hydrogen donor than any other alcohol assayed. Thus, Δ^1-5α-3-ketone I was quantitatively hydrogenated in 3 hr at 80°, while cyclohexanol and 3-pentanol gave rise to only 5% reduction at 100°. Unchanged starting compound was recovered after a similar treatment with 1-butanol and allyl alcohol.

On the contrary, only 25% of the trisubstituted double bond in testosterone (II) was hydrogenated even with benzyl alcohol at 100°. Also the 5,6 double bond survived these reaction conditions. Thus, III and IV were quantitatively converted into 17α-pregn-5-ene-3β,17-diol and 3β-hydroxy-5-pregnen-20-one, respectively, by selective hydrogenation. The role of steric hindrance was further shown by the behavior of tetrasubstituted 16,17-ene in 3β-hydroxy-16-methyl-5,16-pregnadien-20-one (V), which, unlike IV, was recovered unchanged after similar processing.

The promising selectivity of the procedure is further emphasized by the results obtained on $\Delta^{1,4}$-3-ketone VI and $\Delta^{4,6}$-3-ketone VII, both converted in high yield (70–80%) into Δ^4-3-ketone II. Such separation in reactivity of double bonds in $\Delta^{1,4}$-3-ketones toward heterogeneous catalytic hydrogenation is almost unprecedented and strikingly parallels that observed in homogeneous hydrogenations catalyzed by tris(triphenylphosphine)-chlororhodium.[4,5] However, reduction of Δ^4-3-ketone by benzyl alcohol gave rise to isomeric mixtures mainly compounded by 5β epimer, while homogeneous catalytic hydrogenation has been reported to afford exclusively the 5α epimer.[5,6]

Experimental Section

Uv spectra were determined in 95% EtOH with an Optica CF_4 spectrometer; ir spectra were measured in a Nujol mull on a Perkin-Elmer 457 instrument. Tlc was run with 9:1 benzene–acetone on 250-μ-thick layers of silica gel (Carlo Erba, Milan, Italy), containing 1% fluorescence indicator (S5 grün/1, Leuchstoffwerk Gmbh and Co., Heidelberg, West Germany). After a preliminary examination under short-wave uv light (254 mμ), spots were visualized by spraying with 1:1 H_2SO_4–EtOH and heating at 110° for 10 min. Identification of products relied on tlc behavior, mixture melting point, optical rotation, and superimposable uv and ir spectra. Reduction percentages were calculated by uv analysis and semiquantitative tlc.

General Hydrogenation Procedure.—To a solution of the unsaturated steroid (1 g) in the appropriate carbinol (30 ml), 10% Pd on carbon (0.4 g) was added and the resulting suspension was kept under stirring for 3 hr at 80–100°. After removal of the catalyst by filtration and elimination of the alcohol under reduced pressure, the reaction product was isolated in the conventional manner. Recoveries ranged from 90 to 100%.

Registry No.—Benzyl alcohol, 100-51-6.

(4) See C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, **88**, 4537 (1966), and ref 8–11 therein.
(5) A. J. Birch and K. A. M. Walker, *J. Chem. Soc. C*, 1894 (1966).
(6) W. Voelter and C. Djerassi, *Chem. Ber.*, **101**, 58 (1968).

Evidence for a Cationic Imine Intermediate in N,N-Disubstituted α-Aminonitrile Formation[1]

JAMES W. STANLEY,[2] JAMES G. BEASLEY, AND IAN W. MATHISON*

Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103

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α-Aminonitriles are important intermediates in the synthesis of amino acids[3] and sterically hindered amines.[4–7] They may be prepared in one step by treatment of an aldehyde or ketone with NaCN and NH_4Cl (Strecker synthesis). Salts or primary and secondary amines may be used instead of NH_4^+ to obtain N-substituted and N,N-disubstituted α-aminonitriles (I).[8]

Alternatively, they may be prepared by treating

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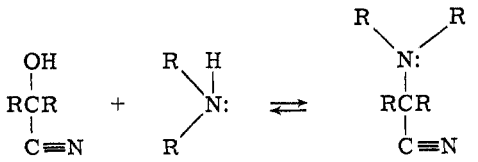
(2) American Foundation for Pharmaceutical Education Fellow, 1970–1972. The work in this paper constitutes a segment of the thesis to be submitted by James W. Stanley to the Graduate School—Medical Sciences of the University of Tennessee in partial fulfillment of the requirements for the degree of Doctor of Philosophy.
(3) "Organic Syntheses," Wiley, New York, N. Y.: Collect. Vol. I, pp 21, 355; Collect. Vol. III, pp 66, 84, 88, 275; Collect. Vol. IV, pp 25, 43, 274.
(4) J. Sansoulet and C. Tackx, *C. R. Acad. Sci.*, **250**, 4370 (1960).
(5) W. H. Taylor and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1960 (1960).
(6) M. Velghe, *Bull. Sci. Acad. Roy. Belg.*, II, 301 (1925).
(7) P. Bruylants, *ibid.*, II, 261 (1925).
(8) D. B. Luten, *J. Org. Chem.*, **3**, 588 (1938).

SCHEME I



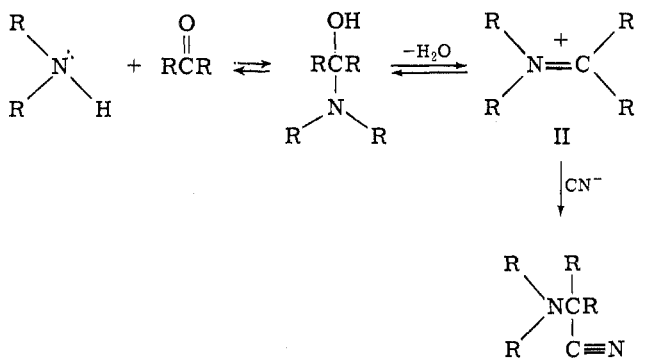
I

the cyanohydrin with the appropriate amine (Scheme I).[9]

Ogata and Kawasaki recently presented evidence of a Schiff base intermediate in the reaction of ring-substituted anilines or primary alkylamines with benzaldehyde.[10] These results supported an earlier report by Stewart and Li[11] that direct displacement of the hydroxyl group of the cyanohydrin was unlikely in the presence of amines.

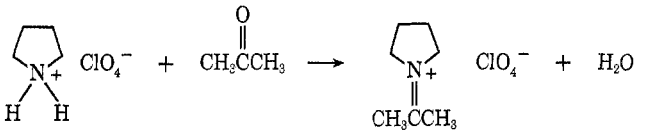
A possible intermediate in the formation of α-aminonitriles from secondary amines is the cationic imine (>C=N<)$^+$(II) (Scheme II).

SCHEME II



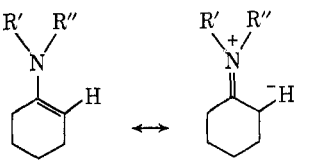
This species is highly reactive to nucleophiles such as the cyanide ion.[12] Accordingly, we selected reactants and conditions that would demonstrate graded differences in their ability to form the proposed cationic imine intermediate II; in particular, we studied acetone and its cyanohydrin with some representative amines, piperidine, morpholine, pyrrolidine, diethylamine, and dimethylamine. A comparison of these amines is particularly pertinent, since their ability to demonstrate exocyclic double bond character is markedly different.[13] Pyrrolidine, morpholine, and piperidine are known to react with aldehydes and ketones to give products that proceed through cationic imine intermediates.[14,15] The order of reactivity is pyrrolidine > morpholine > piperidine, pyrrolidine being by far the most reactive.[16] For example, while pyrrolidine perchlorate will react with anhydrous acetone to yield *N*-isopropylidene pyrrolidinium perchlorate almost quantitatively[17] (Scheme III), the

SCHEME III[17]



piperidine perchlorate salt will not react under similar conditions.[18] This reactivity difference is well known in enamine chemistry where piperidine does not form enamines to the same extent as other amines.[19] This difference in reactivity is attributed to the relative stability of exocyclic double bonds in five- and six-membered rings.[20-22] This application of Brown's generalization for cationic imines is not without precedent. Gurowitz and Joseph[23] have correlated the extent of exocyclic double bond character with vinyl proton absorption in the nmr spectra of some analogous enamines (Chart I). The pyrrolidine enamines dem-

CHART I[a]



[a] Strong overlap of the lone pair on nitrogen with the double bond leads to delocalization as shown above. This causes an upfield shift of the proton on the carbon bearing the charge (from ref 13).

onstrate considerable exocyclic double bond character, whereas the morpholine and piperidine derivatives show much less. Thus one would expect reactivity of N,N-disubstituted aminonitrile formation to parallel the established order of double bond character if the formation of a cationic imine is the rate-determining intermediate.

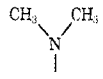
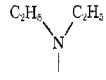
Results and Discussion

The observed order of reactivity was indeed pyrrolidine > morpholine > piperidine, correlating with the extent of exocyclic double bond character (see Table I). The *magnitude* of the reactivity differences supports the proposed rate-determining step as being the formation of a cationic imine. While this is in agreement with Brown's generalization, it was felt that the differences in reactivity were greater than could be explained simply by the nature of the ring interactions resulting from exocyclic double bonds.[24] Some observations from alkene chemistry are pertinent in this respect. In methylenecyclohexane the ethylenic hydrogen atom syn to the 2-equatorial proton is slightly

(9) R. A. Jacobson, *J. Amer. Chem. Soc.*, **67**, 1996 (1945); **68**, 2628 (1946).
(10) Y. Ogata and A. Kawasaki, *J. Chem. Soc. B*, 325 (1971).
(11) T. D. Stewart and C. Li, *J. Amer. Chem. Soc.*, **60**, 2782 (1938).
(12) N. J. Leonard and A. S. Hays, *ibid.*, **78**, 1984 (1956).
(13) W. D. Gurowitz and A. Joseph, *Tetrahedron Lett.*, **No. 49**, 4433 (1965).
(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 972.
(15) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. II, Wiley, New York, N. Y., 1969, p 354.
(16) G. Stork, A. Brizzolna, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(17) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 302 (1963).
(18) The procedures outlined in ref 17 were used unsuccessfully in the attempted preparation of the *N*-isopropylidene piperidinium perchlorate, although the pyrrolidine derivative was easily obtained by simply adding the perchlorate salt of the amine to anhydrous acetone and swirling.
(19) J. Szmuskovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, Interscience, New York, N. Y., 1963, p 10.
(20) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **76**, 467 (1954).
(21) H. C. Brown, *et al.*, *ibid.*, **73**, 212 (1951).
(22) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).
(23) W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).
(24) R. B. Turner and R. H. Garner, *J. Amer. Chem. Soc.*, **80**, 1424 (1958).

TABLE I

PREPARATION OF N,N-DISUBSTITUTED α-AMINONITRILES

Compd	Amine	Time, hr	Yield,[a] %	Bp, °C (mm)	Formula	C, %	H, %	N, %
1		*b*	100	32–34[c] (0.6–0.8)	$C_8H_{14}N_2$	C 69.52 F 69.22	C 10.21 P 10.25	C 20.27 F 20.48
2		<1[d]	98	52–54[e] (20)	$C_6H_{12}N_2$	C 64.24 F 64.02	C 10.78 F 10.52	C 24.72 F 24.94
3		24	93	69–70[f] (1.5)	$C_5H_{14}N_2O$	C 62.31 F 62.05	C 9.15 F 9.33	C 18.16 F 17.94
4		24	70	46–48[g] (0.6–0.8)	$C_9H_{16}N_2$	C 71.01 F 71.02	C 10.59 F 10.64	C 18.40 F 18.23
5		24	59	71–74[h] (20)	$C_8H_{16}N_2$	C 68.52 F 68.40	C 11.50 F 11.30	C 19.98 F 19.70

[a] Yields reported are those of distilled product. [b] Reacts violently to give, in a matter of seconds, quantitative yields. [c] Lit. bp 75° (12 mm), 88.7%: R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949). [d] Reacts exothermically to give product in minutes. [e] Lit.[7] bp 50° (20 mm), 87.6%. [f] Lit. bp 123–125° (21 mm): R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, **72**, 2804 (1950). [g] Lit.[4,7] mp 44–46°; bp 93–94° (14 mm), 70.7%. [h] Lit.[7] bp 66–68° (14 mm), 58.6%.

closer than the usually accepted van der Waals H–H distance (2.5 Å).[25,26] However, the interaction is only a slight repulsion of about 0.2–0.4 kcal/mol. On the other hand, in the case where the hydrogens are replaced by methyl groups (*i.e.*, isopropylidenecyclohexane) there is a larger steric interaction and here the energy of nonbonded interactions between the methyl groups and the 2-equatorial H atoms may be close to twice that of *cis*-2-butene or 2.6 kcal/mol.[27] (Conformational inversion has no meaning here since it leads to the same molecule.) This observation is particularly relevant since one would expect similar steric requirements for formation of a formal $(>C{=}N<)^+$ species. Thus, this factor alone could account for approximately a 100-fold difference in reactivity between piperidine and pyrrolidine,[28] since the latter shows little steric interactions of this type, as evidenced from inspection of Dreiding models. It is important to note that both factors, ring interactions and nonbonded steric interactions, tend to destabilize the piperidine intermediate.

Pyrrolidine, however, appears to be uniquely capable of satisfying the strict steric requirements, thus making additional factors, such as hyperconjugation[29,30] and optimal hybridization of the nitrogen atom, possible contributors to the stability of this intermediate. The combination of these factors may account for the large reactivity differences. The relative contribution of these factors would be of interest and in this regard the results with dimethylamine and diethylamine are useful. Dimethylamine, although less reactive than pyrrolidine, is considerably more reactive than the remaining amines. Ring interactions seem to retard piperidine reactivity relative to dimethylamine while diethylamine appears to be less reactive than dimethylamine because of fairly severe nonbonded steric interactions.

The intermediate reactivity of morpholine may be attributed to a dual role by the oxygen in the ring, reducing the number and degree of unfavorable conformational interactions in relation to piperidine as well as stabilizing the positive charge generated by the cationic imine intermediate.

Thus while in fundamental agreement with previous findings on the intermediate involved in α-aminonitrile formation with primary amines, the reaction with secondary amines and ketones includes an important steric parameter, that being the ability to form a cationic imine.

Experimental Section

All compounds reported demonstrated characteristic spectra of α-aminonitriles, ir ($CHCl_3$) 2220 (C≡N, weak), nmr ($CDCl_3$) δ 1.50 (s, 6 H, $-CH_3$), as well as satisfactory analytical data (±0.3% for C, H, N) performed by Galbraith Laboratories, Knoxville, Tenn.

General Procedure.—The formation of the α-aminonitriles was conducted in the same manner for all compounds. The appropriate amine (0.230 mol) was mixed with 20 ml of acetone in a 100-ml round-bottom flask and stirred with a magnetic stirrer. After approximately 2 min acetone cyanohydrin (0.230 mol) was added and the flask was tightly stoppered and allowed to stir for the period indicated in Table I. Work-up involved removal of solvent under vacuum followed by immediate vacuum distillation to yield the product, which in all cases was a colorless oil. The yields obtained are outlined in Table I.

Starting Materials.—Acetone, A. R. (Mallinckrodt), was purified according to Vogel.[31] Acetone cyanohydrin (Aldrich Chemical Co.) was distilled before use to yield a clear, colorless liquid, bp 80–82° (15 mm). The anhydrous amines (Eastman) were dried over KOH and distilled before use.

Registry No.—**1**, 35666-79-6; **2**, 2273-40-7; **3**, 35666-81-0; **4**, 2273-41-8; **5**, 35672-46-9.

(25) L. S. Bartell, *J. Chem. Phys.*, **32**, 827 (1960).
(26) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 501 (1966).
(27) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(28) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 207.
(29) A. Streitwieser, *J. Amer. Chem. Soc.*, **77**, 6713 (1955).
(30) V. J. Shiner, *ibid.*, **78**, 2654 (1956).
(31) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956, p 171.