1.5 equiv of organocuprate(I) is used.[16] Third, organolithium reagents are generally less readily available than organomagnesium reagents.[17] Finally, secondary and tertiary alkylcopper reagents are generally more difficult to prepare than primary ones.[1,17] The functional group specificity (Table I) and the simplicity and mildness of experimental conditions, however, make synthesis of ketones from acid chlorides and organocopper reagents a useful new synthetic method.[18]

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(16) Although cuprous ion "catalyzed" Grignard reaction with acid chlorides to form ketones has been reported, it appears that the ratio of copper to RMgX is 1.6:1.0; see J. E. Dubois and M. Boussu, *Tetrahedron Lett.*, 2523 (1970), and J. E. Dubois, M. Boussu, and C. Lion, *ibid.*, 829 (1971); see also J. A. MacPhee and J. E. Dubois, *ibid.*, 467 (1972).

(17) Organocopper reagents derived from Grignard reagents and cuprous iodide have recently been used to effect conversion of *cis*-4-*tert*-butylcyclohexanecarbonyl chloride to the corresponding aryl and *tert*-butyl ketones without epimerization at the α carbon; see N. T. Luong-Thi, H. Rivière, J. P. Bègnè, and C. Forrestier, *Tetrahedron Lett.*, 2113 (1971).

(18) G. H. Posner and C. E. Whitten, *Org. Syn.*, submitted for publication (procedure currently being checked).

(19) NDEA Fellow, 1969–present.

Gary H. Posner,* Charles E. Whitten,[19] Paul E. McFarland
Department of Chemistry, The Johns Hopkins University
Baltimore, Maryland 21218

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Dimethyl Sulfoxide–Water for Study of "Unobservable" General Base Catalysis and Anomalous Behavior of Hydroxide Ion[1]

Sir:

The data of this communication respond to two important questions which arise in studies of acid–base systems: (a) are there carbon acids which behave like normal oxygen and nitrogen acids in all respects, including their reaction with hydroxide ion, and (b) does the frequently observed anomalously slow reaction rate of hydroxide ion with carbon acids reflect a different degree of proton transfer in the transition state?

Eigen[2] has shown that reactions of major categories of acids and bases in aqueous solution exhibit a "normal" behavior in which the thermodynamically favored proton transfer occurs at a diffusion-controlled rate, *i.e.*, with a rate independent of the strength of the catalyst and hence with a Brønsted coefficient of 0. The reverse process then occurs with a Brønsted coefficient of unity. Deviation from this normal behavior usually occurs only in a transition region of a few pK units close to $\Delta pK = 0$, where ΔpK gives the pK difference for catalyst and substrate.

Carbon acids often depart widely from this behavior in that they exhibit intermediate Brønsted coefficients (0.4–0.8) for wide ranges and large values of ΔpK.[3,4] However, a recently studied group of cyanocarbon acids exhibits almost normal behavior in that their proton removal involves general base catalysis with a Brønsted β of virtually unity and a reverse reaction whose Brønsted α is almost zero and whose rate is within a factor of 10 of that of a diffusion-controlled process.[5–7] A strong implication of these results, which is confirmed by the observation of small primary hydrogen isotope effects (*ca.* 1.5) for the proton removal reaction, is that in the transition state the proton is virtually entirely transferred. For these cyanocarbon reactions proton removal by hydroxide ion is anomalously slow,[5,6] a behavior which is commonly observed with carbon acids but not with oxygen and nitrogen acids.[2,4]

The experiments which follow compare one of these cyanocarbon acids with chloroform, an acid which on the basis of its structure and also Hine's[8] earlier studies appears to be a good candidate for fully normal acid behavior. As a first experiment, we have compared the primary hydrogen isotope effects for reaction of these two with hydroxide ion, utilizing a new, accurate experimental procedure which involves measuring the rate of tritium uptake by the protio and deuterio compound from a tritiated aqueous solvent. For very small amounts of reaction, the appropriate equation for this procedure is

$$\left(\frac{d\alpha}{dt}\right)^{H}_{t\to 0}\Bigg/\left(\frac{d\alpha}{dt}\right)^{D}_{t\to 0} = (k_1^{OH^-})^{H}/(k_1^{OH^-})^{D}$$

where α is the atom per cent of tritium uptake in the compound. Isotope effects for reaction of such normal bases as morpholine and phenolate ion with the cyanocarbon acid give the small isotope effects of k^H/k^D = 1.7 and 1.4, respectively, indicating a fully transferred proton in the transition state. Reaction of hydroxide ion with this same species shows a primary hydrogen isotope effect of 3.5. Similar experiments utilizing chloroform reacting with hydroxide ion gave a primary isotope effect of 1.42.

A second comparison is the entropy of activation for reaction of the two carbon acids with hydroxide ion. With rate coefficients in M^{-1} sec^{-1} units, ΔS^* for the reaction of hydroxide with the 1,4-dicyanobutene was -10 eu. In contrast, reaction of chloroform and hydroxide ion gives a ΔS^* of $+15$ eu. This latter is about the expected size for a reaction in which a proton is fully transferred from the carbon acid to hydroxide ion.

These results suggest the proton is fully transferred from chloroform to hydroxide ion, whereas with dicyanobutene the transfer is only partial.

Chloroform in aqueous solution revealed no observable catalysis by the general bases pyridine and morpholine. This observation, in conjunction with the results with hydroxide ion, can plausibly be interpreted by assuming that hydroxide ion is reacting in a fully normal way, with a Brønsted β of unity. With an acid as weak as chloroform this would lead to "unobservable general base catalysis," *i.e.*, the hydroxide ion process would effectively overwhelm catalysis by all weaker bases.

As a further comparison of chloroform and dicyanobutene, we have studied the reaction of the two carbon acids with hydroxide ion in the mixed solvent DMSO–H_2O. Bell and Cox[9] have previously utilized this mix-

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(1) Work supported by a grant from the Atomic Energy Commission.

(2) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).

(3) M. L. Bender, "Mechanisms of Homogenous Catalysis from Protons to Proteins," Part I, Wiley-Interscience, New York, N. Y., 1971.

(4) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(5) E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969).

(6) F. Hibbert, E. A. Walters, and F. A. Long, *ibid.*, **93**, 2829 (1971).

(7) F. Hibbert and F. A. Long, *ibid.*, **93**, 2836 (1971).

(8) J. Hine, N. W. Burske, M. Hine, and P. B. Longford, *ibid.*, **79**, 1406 (1957), and earlier papers.

(9) R. P. Bell and B. G. Cox, *J. Chem. Soc. B*, 194 (1970); (b) *ibid.*, 783 (1971).

ture to determine the Brønsted β for the reaction of hydroxide ion with menthone and found $\beta = 0.48$, about as expected for reaction of this ketone in a purely aqueous solvent. Under the plausible assumption that the substrate SH behaves similarly to an H_- indicator acid, it can be shown that a Brønsted or Eigen plot for $k_{\mathrm{OH^-}}$ can be replaced by a plot of this rate coefficient *vs.* the function $H_- + \mathrm{og}\ ([H_2O]/[OH^-])$. This procedure can give general evidence on the behavior of hydroxide ion as a base. More importantly, it permits determination of the Brønsted β in cases where "unobservable" general catalysis is suspected. In the rate studies done here, the two substrates were allowed to react with hydroxide ion at concentrations of from 0.001 to 0.05 *M* utilizing mixed solvents with mole per cent DMSO ranging from 0 to 25%. H_- values were taken from Bowden.[10] The resulting Brønsted coefficient for chloroform is 1.0 within experimental error, whereas that for the 1,4-dicyanobutene is 0.7. This information, combined with the previous data, permits two conclusions. First, for the cyanocarbon acid, the degree of proton transfer to hydroxide ion is only partial, in contrast to the situation with bases like morpholine and phenolate ion, where it is virtually complete. With chloroform, the proton transfer to hydroxide is complete and this, with the other evidence, strongly indicates that this is a case of unobservable general base catalysis, *i.e.*, chloroform is behaving fully normally as an acid in the Eigen sense.

(10) K. Bowden, *Chem. Rev.*, **66**, 119 (1966).

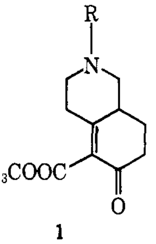
Zafra Margolin, F. A. Long*
Department of Chemistry, Cornell University
Ithaca, New York 14850
Received January 12, 1972

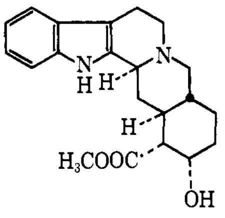
Stereoselective Total Syntheses of (±)-Yohimbine, (±)-ψ-Yohimbine, and (±)-β-Yohimbine

Sir:

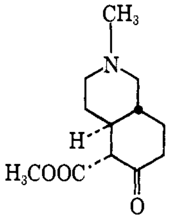
We have for some time considered that hydroisoquinolone carboxylic acids related to **1** might make possible unusually simple syntheses of some of the yohimbe alkaloids. It is indeed this consideration that led us to develop a general method[1] for the fusion of a 2-carboxy-Δ^2-cyclohexenone system to a preexisting ring.

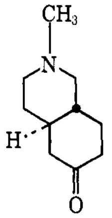
We now describe the synthesis of **1** and its transformation into (±)-yohimbine (**2**).[2]


1


2

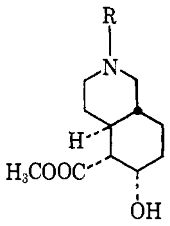
Reaction of the pyrrolidine enamine of *N*-methyl-4-piperidone with methyl 3-oxo-4-pentenoate[3] (3:1 benzene–methanol, reflux, 8 min) gave in ~80% yield the isoquinolone **1**,[4] R = CH_3, as an oil (ir (film) 1739, 1675, and 1634 cm^{-1}; nmr ($CDCl_3$) δ 3.81 (s, CO_2CH_3), 2.33 (s, NCH_3); $\lambda_{\max}^{\mathrm{EtOH}}$ 233.5 nm (ϵ 9355)). Reduction of **1** with lithium (10% excess) in liquid ammonia–ether (4 equiv of *tert*-butyl alcohol) at −78° gave, stereospecifically, the *trans*-hydroisoquinolone ester (**3**), mp 73–74°, ir ($CHCl_3$) 1745, 1712 cm^{-1}. The expected[5] trans stereochemistry was evidenced by the nonenolic character of the β-keto ester system and by acid hydrolysis of **3** to the known *trans*-*N*-methyl decahydroisoquinolone (**4**).[6]

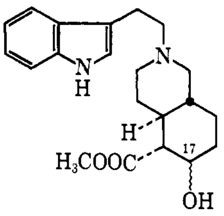

3

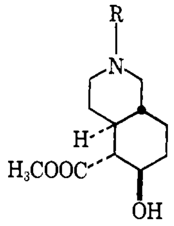

4

Stereoselective reduction of **3** could be achieved with platinum and hydrogen in acetic acid (room temperature, 40 hr) and the resulting mixture of amino alcohols was converted with cyanogen bromide (benzene, room temperature, 1.5 hr) into the mixture of axial and equatorial *N*-cyano alcohols which could be separated by chromatography.

The desired axial isomer **5** (mp 125.5–127°, from benzene) was the major component of the mixture and could be isolated in 42% yield, together with ~30% of the equatorial isomer **6**, mp 152–153.5°. The stereochemistry[7] of the hydroxyl groups in **5** and **6** follows from the nmr of the related acetates (mp 105–106°, δ 5.45, J = ~7 Hz, and mp 118–120°, δ 4.98, J = ~21 Hz, respectively).


5, R = CN
7, R = H


9, 17α-OH
10, 17β-OH


6, R = CN
8, R = H

The secoyohimbane skeleton of **9** was then easily assembled *via* reductive decyanation[8] of **5** (zinc in 82% acetic acid, 100°, 3.5 hr) to the corresponding secondary amino alcohol **7**, mp 159–160° (80% yield, ir 3450 cm^{-1}), which was alkylated with tryptophyl bromide[9] (overnight reflux with 3 equiv of potassium carbonate

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(1) G. Stork and R. Nath Guthikonda, manuscript in preparation.

(2) For other syntheses, see: (a) the classical work of E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Amer. Chem. Soc.*, **91**, 7315 (1969); (b) L. Toke, K. Honty, and Cs. Szantay, *Chem. Ber.*, **102**, 3248 (1969).

(3) *Cf.* I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953). A superior and more general synthesis of this type of substance will be described elsewhere.

(4) All substances described here were purified by chromatography on activity IV neutral alumina and gave analytical and/or spectral data in agreement with the postulated structures.

(5) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1961 (1964).

(6) A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 327 (1956).

(7) *Cf.* E. E. Smissman, J. Pengman Li, and M. W. Cruse, *J. Org. Chem.*, **35**, 1352 (1970).

(8) T. Fehr, P. A. Stadler, and A. Hofmann, *Helv. Chim. Acta*, **53**, 2197 (1970).

(9) T. Hoshino and K. Shimodaira, *Justus Liebigs Ann. Chem.*, **520**, 19 (1935).