fer for a number of ions from their data on non-isothermal cells with silver–silver bromide, and mercury–mercuric oxide electrodes. Their values (Table VI, ref. 1) are dependent upon an assumption concerning the entropy of transfer for large tetraalkylammonium ions, and differ considerably from earlier estimates.[2] Difficulties arise, however, if these values are applied to the calculation of Soret coefficients. It is well-established theoretically[3] that the Soret coefficient $\sigma$ for a uni-univalent electrolyte is given by ignoring corrections for

$$\sigma = \frac{\mathrm{d}\,(\ln c)}{\mathrm{d}T} = -\left[\frac{S_C^* + S_A^*}{2RT}\right]$$

activities. Using Goodrich's values for KBr and KOH, respectively, we obtain at $T = 298°$ A.: $\sigma_{KBr} = +3.9 \times 10^{-3}$; $\sigma_{KOH} = -8.8 \times 10^{-3}$. However, experimental measurements of Soret coefficients show that aqueous solutions of all electrolytes give negative values of $\sigma$. The calculated value for KOH is of the right sign and order of magnitude (*cf.* Tanner[4]), but this is not the case for the KBr value. It is, of course, true that Soret coefficients are difficult to measure, but it seems unlikely that such a difference in sign between bromides and hydroxides would not have been observed if Goodrich's assignment had been correct. It is clear that the experimental work on Soret coefficients requires that the *net* entropy of transfer for a salt must be positive, unless present theoretical views on these non-isothermal phenomena are to be changed.

There is a further, minor, point. We are quoted (Ref. 1, p. 4417) as supporting a value of + 3.6 e.u. for the entropy of transfer of the bromide ion. It is clear from our paper[5] that this value was calculated on Eastman's assumptions in order to test his equation on experimental results from mixed solutions of bromides, and that we attached no other significance to it.

(2) E. D. Eastman, THIS JOURNAL, **50**, 292 (1928).

(3) S. R. de Groot, *J. Phys. Rad.*, [8] **8**, 193 (1947), from the principle of microscopic reversibility; K. Wirtz, *Z. Physik*, **124**, 482 (1948), from a kinetic theory of liquids; L. D. Tuck, *J. Chem. Phys.*, **18**, 1128 (1950), from a thermodynamic method; H. J. V. Tyrrell, unpublished calculations, from the theory of rate processes.

(4) Tanner, *Trans. Far. Soc.*, **23**, 75 (1927).

(5) H. J. V. Tyrrell and G. L. Hollis, *ibid.*, **45**, 411 (1949).

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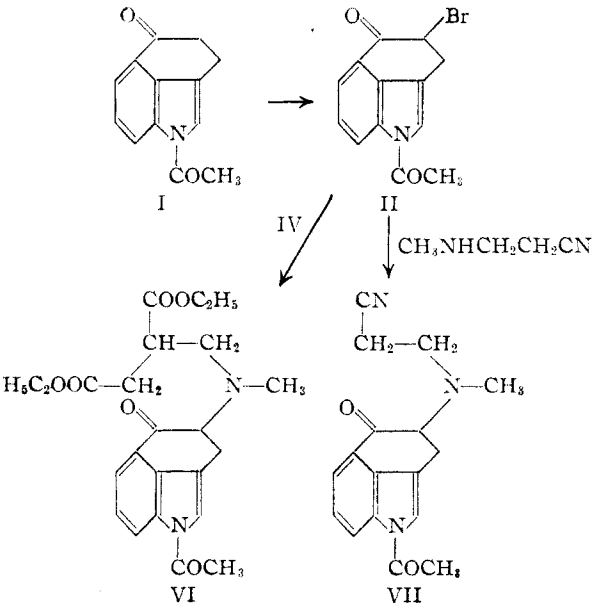
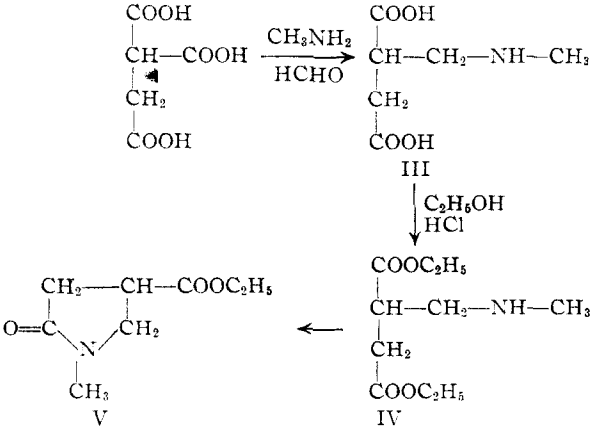
## AMINO DERIVATIVES OF 5-KETO-1,3,4,5-TETRAHYDROBENZ[cd]INDOLE[1]

*Sir:*

In continuation of studies[2] directed toward the total synthesis of the ergoline ring system and of lysergic acid, N-acetyl-5-keto-1,3,4,5-tetrahydrobenz[cd]indole, I, m.p. 148–149° (*Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57; N-acetyl, 20.18. Found: C, 72.95; H, 5.24; N, 6.37; N-acetyl, 20.44) has been converted to the 4-bromo-derivative, II, m.p. 162–163° (*Anal.* Calcd. for $C_{13}H_{10}NO_2Br$: C, 53.44; H, 3.45; N, 4.79; Br, 27.35. Found: C, 53.58; H, 3.67; N, 4.71; Br, 27.70).




α-Carboxysuccinic acid has been allowed to react with methylamine and formaldehyde in aqueous solution to yield the amino acid III, m.p. 166–168° (*Anal.* Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.81; H, 6.91; N, 8.82) which has been converted with hydrogen chloride in absolute ethanol to the hydrochloride of the amino ester IV, m.p. 70–71° (*Anal.* Calcd. for $C_{10}H_{20}NO_4Cl$; C, 47.33; H, 7.95; N, 5.52; Cl, 13.97. Found: C, 47.08; H, 7.90; N, 5.86; Cl, 13.94; *p*-toluenesulfonamide, m.p. 51–52°, *Anal.* Calcd. for $C_{17}H_{25}NO_6S$: C, 54.97; H, 6.78; N, 3.77. Found: C, 54.61; H, 6.69; N, 4.02; pyrrolidone, V, b.p. 167–168°/20.5, *Anal.* Calcd. for




$C_8H_{13}NO_3$: C, 56.12; H, 7.65. Found: C, 56.10; H, 7.55, $d^{20}_{20}$ 1.1170, $n^{25}D$ 1.4620, $M_D$ calcd.: 42.43; $M_D$ found: 42.13).

Condensation of II with IV has afforded the amino ketone VI, isolated as the picrate, m.p. 158–160° (*Anal.* Calcd. for $C_{29}H_{31}N_5O_{13}$; C, 52.97; H, 4.75; N, 10.65; N-acetyl, 6.55. Found: C, 53.56; H, 4.71; N, 10.85; N-acetyl, 7.14). II with β-methylaminopropionitrile has yielded VII, m.p. 128–129° (*Anal.* Calcd. for $C_{17}H_{17}N_3O_2$: C,

(1) This investigation was supported in part by a research grant from The United States Public Health Service.

(2) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

69.13; H, 5.80; N, 14.23; N-acetyl, 14.57. Found: C, 69.48; H, 6.10; N, 14.23; N-acetyl, 14.37). Intramolecular cyclization of VI and subsequent decarboxylation, as well as further transformations of VII and related substances, will be reported shortly.

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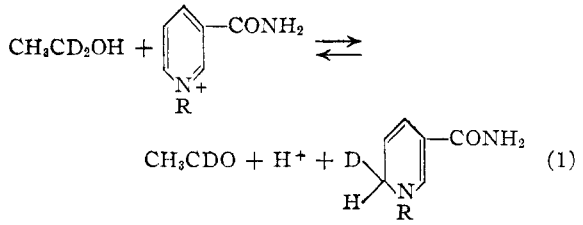
RECEIVED FEBRUARY 15, 1951

## THE ENZYMATIC TRANSFER OF HYDROGEN FROM ALCOHOL TO DPN

*Sir:*

The oxidation of ethyl alcohol to acetaldehyde by DPN (diphosphopyridine nucleotide) in the presence of alcohol dehydrogenase has been investigated with deuterium as a tracer. It has been found that a hydrogen atom is transferred directly from the alpha carbon atom of the alcohol to the DPN molecule (see Equation 1) and therefore that the hydrogen atoms of the solvent (water) do not enter the reduction product.




(1)

where R represents the ribose-pyrophosphate-ribose-adenine groups of DPN. (Equation 1 is illustrated above with Karrer's structure[1] for reduced DPN).

$CH_3CD_2OH$ was prepared by the reduction of phenyl acetate with lithium aluminum deuteride; the procedure was analogous to that used for making $CH_3CDOHCH_3$.[2] (*Anal.*[3] Deuterium atoms/molecule: calcd. 2.0, found 2.1). The deuteroalcohol (0.2 cc.) was equilibrated for 30 minutes with 4 mg. of crystalline alcohol dehydrogenase[4] and 0.05 g. of DPN of 93% purity[5] in 5 cc. of 0.5 *M* aqueous $(HOCH_2)_3CNH_2$ buffer[6] at *p*H 9.0. The enzyme was heat inactivated and removed by precipitation with 10 cc. of alcohol. Then 45 cc. of alcohol and 0.4 cc. of 6 *N* HCl were added to precipitate the reduced DPN, which was redissolved in 1 cc. of the buffer at *p*H 7.4, and reprecipitated with 15 cc. of alcohol. The purpose of the reprecipitation was to remove any exchangeable deuterium. *Anal.* Found: C, 38.45; H, 6.36; deuterium atoms per molecule, 1.1. Calculation of the last figure was based on the hydrogen analysis of the isolated amine salt, which contained approximately 65 atoms of hydrogen present per molecule of enzymatically active pyridine nucleotide.

(1) P. Karrer, B. H. Ringier, J. Büchi, H. Fritzsche and U. Solmssen, *Helv. Chim. Acta*, **20**, 55 (1937); P. Karrer and O. Warburg, *Biochem. Z.*, **285**, 297 (1935).

(2) A. Leo, unpublished results.

(3) R. B. Alfin-Slater, S. M. Rock and M. Swislocki, *Anal. Chem.*, **22**, 421 (1950).

(4) E. Racker, *J. Biol. Chem.*, **184**, 313 (1950).

(5) A. Kornberg and B. L. Horecker, private communication.

(6) G. Gomori, *Proc. Soc. Exptl. Biol. Med.*, **62**, 33 (1946).

Identical results were obtained when the procedure above was repeated with twice the concentration of enzyme and twice the equilibration period. The results were also confirmed by the following control experiments. The procedure was repeated with unlabeled ethyl alcohol in a medium of $D_2O$, and the reduced DPN was found to contain no excess deuterium. Reduced DPN was also prepared by chemical reduction[7] with $Na_2S_2O_4$ in $D_2O$, and precipitation with ethyl alcohol. The product was dissolved in $H_2O$ and reprecipitated. *Anal.* Deuterium atoms per molecule; found, 1.0. Repetition of the solution and precipitation procedure did not change the deuterium content of the reduced DPN; the deuterium atom in the molecule therefore does not exchange with hydrogen atoms of the solvent at neutral *p*H.

The rate of the enzymatic reduction of DPN by deuteroalcohol, the stereochemistry of the reduction, and other aspects of this problem are currently under investigation.

We wish to thank Dr. P. Ofner, who carried out the purification of the DPN and Dr. H. S. Anker, who assisted with some of the mass spectrometer analyses.

(7) P. Ohlmeyer, *Biochem. Z.*, **297**, 66 (1938).

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RECEIVED MARCH 19, 1951

## THE TOTAL SYNTHESIS OF A STEROID[1]

*Sir:*

We wish to record the total synthesis of methyl *dl*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (IV). This represents the first synthesis of a compound possessing the full hydroaromatic steroid nucleus of the correct stereochemical configuration.

Condensation of 5-methoxytoluquinone with butadiene in benzene gave *cis*-1,4-diketo-2-methoxy - 4a - methyl - 1,4,4a,5,8,8a - hexahydronaphthalene (m.p. 94.5–95.5°).[2] The latter was transformed, by acidification of its solution in basic aqueous dioxane under carefully controlled conditions, to the *trans*-isomer (m.p. 130–131°, found, C, 69.38; H, 6.85). Reduction with lithium aluminum hydride gave the corresponding glycol (m.p. 139–140°, found, C, 68.78; H, 8.77), transformed by dilute mineral acid in aqueous dioxane to 1-hydroxy-2-keto-4a-methyl-1,2,4a,5,8,8a-hexahydronaphthalene (m.p. 71.5–72.5°). Acetylation, followed by treatment with zinc in boiling acetic anhydride or xylene, gave the *trans*-bicyclic ketone (I) (b.p. 75° at 0.2 mm., m.p. 34–35°, max. 224 mμ (log $E$ = 4.01), found, C, 81.02; H, 8.98). This was converted to the hydroxymethylene ketone (b.p. 88–90° at 0.015 mm., max. 229 mμ (4.00) and 361 mμ (3.88)), which with ethyl vinyl ketone in the presence of potassium *t*-butoxide in *t*-butanol yielded 1-formyl-1-γ-ketopentyl-2-keto-4a - methyl - 1,2,4a,5,8,8a - hexahydronaphthalene (m.p. 97.5–98.5°, found, C, 74.43; H, 8.15).

(1) First announced at the Centenary Lecture of the Chemical Society presented at Burlington House, London, on April 26, 1951.

(2) Orchin and Butz, *J. Org. Chem.*, **8**, 509 (1943).