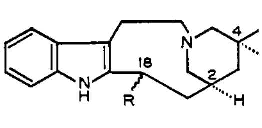
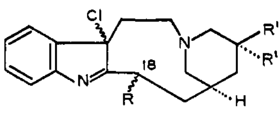
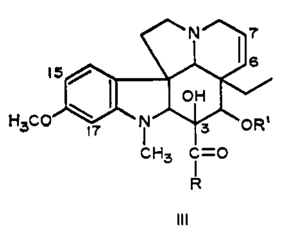


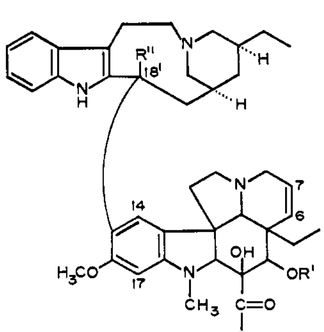
I



II



III



IV

R'' = $COOCH_3$), and for this reason its introduction during any dimerization process would be an important step in subsequent syntheses of these substances. For this purpose, the previously unknown chloroindolenine of carbomethoxy-4β-dihydrocleavamine (II, R = $COOCH_3$; R' = H; R'' = CH_2CH_3), obtained as an amorphous solid by the method previously reported,[4,5] was allowed to react with vindoline (III, R = OCH_3; R' = CH_3CO) in refluxing anhydrous methanol containing 1.5% hydrogen chloride. The resulting product from this reaction was dimer IV (R = OCH_3; R' = CH_3CO; R'' = $COOCH_3$) isolated as an amorphous powder, in 45% yield. High-resolution mass spectrometry[6] established the formula, $C_{46}H_{58}O_8N_4$ (found: mol wt, 794.419; calcd: mol wt, 794.425), while spectral and chemical evidence conclusively established structure IV for this compound. The uv spectrum [λ_{max}^{MeOH} mμ (log ε) 265 (4.22), 287 (4.19), 296 (4.17), 310 (sh, 3.97)] was in excellent agreement with expectation,[7] while the nmr spectrum[8] was so instructive in this and the other series mentioned later that it virtually proved the structure on its own merits. In all instances, the spectrum was a summation of the signals characteristic of the individual monomeric units. Thus, for the above dimer, the following nmr signals were observed: 2.55–3.15 (4 H, aromatic, cleavamine portion), 3.05 (1 H, singlet, $C_{14}H$, vindoline portion), 4.04 (1 H, singlet, $C_{17}H$, vindoline portion), 6.27 (3 H, singlet, $COO\mathit{CH}_3$ at $C_{18'}$), 9.09 (3 H, triplet, $CH_2\mathit{CH}_3$, cleavamine portion), 9.34 (3 H, triplet, $CH_2\mathit{CH}_3$, vindoline portion). Chemical evidence in support of IV became available when mild cleavage of this dimer (1.5 *N* methanolic HCl, Sn, $SnCl_2$) afforded the starting monomers, carbomethoxy-4β-dihydrocleavamine and vindoline.

The generality of the dimerization reaction was further demonstrated when other novel dimeric systems necessary for biological evaluation as possible antitumor agents were synthesized. The above chloroindolenine, when allowed to react with deacetylvindoline hydrazide[9] (III, R = $NHNH_2$; R' = H), provided the desired $C_{18'}$-carbomethoxy dimer IV (R = $NHNH_2$; R' = H; R'' = $COOCH_3$), $C_{43}H_{56}N_6O_6$ (found: mol wt, 752.427; calcd: mol wt, 752.426), as an amorphous powder in 25% yield. This substance exhibited the following spectral properties: λ_{max}^{MeOH} mμ (log ε) 264 (4.11), 290 (4.06), 296 (4.05), 313 (sh, 3.87); nmr signals: 2.48–3.10 (4 H, aromatic, cleavamine portion), 3.06 (1 H, singlet, $C_{14}H$, vindoline portion), 4.07 (1 H, singlet, $C_{17}H$, vindoline portion), 6.30 (3 H, singlet, $COO\mathit{CH}_3$ at $C_{18'}$), 9.08 (3 H, triplet, $CH_2\mathit{CH}_3$, cleavamine portion), 9.20 (3 H, triplet, $CH_2\mathit{CH}_3$, vindoline portion). Cleavage of this molecule under the abovementioned conditions provided carbomethoxy-4β-dihydrocleavamine and deacetylvindoline hydrazide, identified by comparison with authentic samples.

In a similar fashion, the dimer IV (6,7-dihydro; R = OCH_3; R' = CH_3CO; R'' = $COOCH_3$), $C_{46}H_{60}O_8N_4$ (found: mol wt, 796.441; calcd: mol wt, 796.441), from the reaction of the chloroindolenine and dihydrovindoline (III, 6,7-dihydro; R = OCH_3; R' = CH_3CO) was obtained as an amorphous solid in 42% yield. The spectral properties of this compound were similar to those presented above for the other dimers, while mild cleavage into the starting monomers again provided indisputable evidence for the assigned structure.

Using methods analogous to those applied to the $C_{18'}$-carbomethoxy dimers as discussed above, we also prepared dimer IV (R = $NHNH_2$; R' = R'' = H) in 77% yield and dimer IV (R = OCH_3; R' = CH_3CO; R'' = H) in 68% yield utilizing the chloroindolenine II (R = R' = H; R'' = CH_2CH_3). The former compound has been recently reported in an independent investigation by the Lilly group.[10]

The above dimerization provides the first synthesis of dimeric systems bearing the desired ester function at $C_{18'}$ known to be present in the Vinca alkaloids. It is hoped that this reaction will find application in the laboratory synthesis of the natural dimers.

Acknowledgment. Financial aid from the National Cancer Institute of Canada, National Research Council of Canada, and Medical Research Council of Canada is gratefully acknowledged.

---

(5) Complete characterization of this intermediate will be reported in our detailed paper.

(6) High-resolution mass measurements were performed on an AEI MS9 mass spectrometer. In all instances, mass measurements were made at several masses to confirm these results.

(7) N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids," Lilly Research Laboratories, Indianapolis 6, Ind., 1960.

(8) All nmr spectra were determined on a Varian HA-100 spectrometer. The values are given in τ units.

(9) N. Neuss, M. Gorman, W. Hargrove, N. J., Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.*, **86**, 1440 (1964).

(10) N. Neuss, M. Gorman, N. J. Cone, and L. L. Huckstep, *Tetrahedron Letters*, 783 (1968).

James P. Kutney, John Beck, Feike Bylsma, Walter J. Cretney
Chemistry Department, University of British Columbia
Vancouver 8, Canada

Received March 8, 1968

Reactions of Aromatic Radical Anions. II. A Moderate-Temperature Reaction of Sodium Naphthalene and Molecular Hydrogen

Sir:

Whereas present schemes for the preparation of sodium hydride employ the high-temperature reaction of sodium metal and hydrogen,[1,2] we wish to report

---

(1) G. W. Mattson and T. P. Whaley, *Inorg. Syn.*, **5**, 10 (1957).

(2) The absorption of hydrogen by sodium is reported to begin at about 200°: D. T. Hurd, "An Introduction to the Chemistry of Hydrides," John Wiley and Sons, New York, N. Y., 1952, p 31.

that hydrogen is absorbed at temperatures from 25 to 40° at 1 atm by tetrahydrofuran solutions of sodium naphthalene. Sodium hydride in an exceedingly reactive form is the product of the reaction.

The current study was initiated with the view that in large part the difficulty with the sodium–hydrogen reaction is the protective film of solid sodium hydride covering the sodium.[2] Indeed special means to disperse the sodium improve the yield and lower the required temperature.[3] A successful low-temperature reaction of sodium and hydrogen requires that the sodium be present in a very highly dispersed form and equally important that the reduction potential of the system be sufficient for facile reaction. These requirements suggested the use of sodium naphthalene. Since sodium naphthalene is essentially molecularly dispersed, surface problems are eliminated. Moreover, encouraged by the recent demonstrations of the powerful electron-transfer properties of this reagent,[4,5] we sought to activate molecular hydrogen at moderate temperatures.

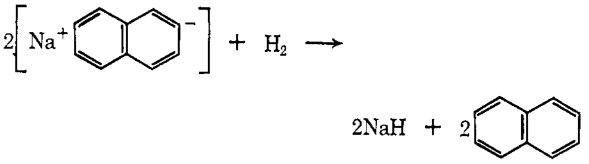
The reaction of sodium naphthalene (50 mmol) in tetrahydrofuran with hydrogen at 40° was conducted using a modified B^2 hydrogen generator.[6] The radical anion solution was prepared under N_2 in a three-necked round-bottom flask in place of the usual hydrogenation flask, and a drying tube was placed between the hydrogen generator and the reaction flask. Reaction was followed both by the uptake of hydrogen and by assaying the radical anion concentration in the reaction vessel.[7] Over a 60-hr period 25 mmol of hydrogen was absorbed and the concentration of radical anion went to zero. The reaction rate is very sensitive to the stirring rate as expected for a two-phase reaction, and, since the magnetically driven glass stirring bar affords only minimal efficiency, we expect shorter reaction times in the more efficiently stirred reactions, which we are presently devising. The solid product was separated by centrifugation and found to be highly pyrophoric. A sample of the solid was allowed to react with water in a gas displacement apparatus to give hydrogen, and the resulting solution was titrated with standard acid. The ratio of H_2:NaOH obtained (0.93) is close to the value of 1.0 required by eq 1. The yield based on H_2 is greater than 90%.

$$NaH + H_2O \longrightarrow H_2 + NaOH \qquad (1)$$

Conclusive evidence that highly active sodium hydride was the product was afforded by quenching the entire reaction mixture directly with deuterium oxide and analyzing the resulting gas by mass spectrometry. In control experiments we have shown that under these conditions sodium metal gives predominantly D_2, and authentic sodium hydride (Metal Hydrides, Inc.) gives predominantly HD. The product of the sodium naphthalene–hydrogen reaction gave predominantly HD (85%),[8] thus confirming that the principal product is indeed sodium hydride, as predicted.

The reaction involves electron transfer, evidenced by the fact that the naphthalene is recovered quantitatively. Our analytical method based on gas chromatography with internal standards would have detected 0.2% dihydronaphthalenes or tetralin, the expected products of naphthalene if sodium naphthalene functioned as a nucleophile in this reaction. Significantly, electron transfer to nitrogen has been observed with sodium naphthalene in the presence of titanium alkoxides.[5]

While the actual scheme probably involves several steps, our results suggest stoichiometric reaction given by eq 2.



(2)

As regards the intervening steps, it is only clear that naphthalene is inert. Of greater interest 1-octene is also inert when present during and after the hydrogenation of sodium naphthalene, and the yield of sodium hydride is unaffected. Further speculation about the mechanism must await the results of experiments in progress.

Not only is the present reaction a more convenient procedure, but it also produces sodium hydride in an exceedingly active form. In preliminary experiments we have observed that it converts cyclohexanone to the enolate rapidly at room temperature. We are presently exploring its use as a catalyst and reagent for a variety of reactions.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation. We especially wish to thank Professor Kevin T. Potts (Rensselaer Polytechnic Institute) for his invaluable assistance in the determination and analysis of the mass spectra.

---

(3) A. M. Muckenfuss, U. S. Patent 1,958,012 (May 8, 1934).

(4) (a) W. D. Closson, P. Wriede, and S. Bank, *J. Am. Chem. Soc.*, **88**, 1581 (1966); (b) G. D. Sargent, J. N. Cron, and S. Bank, *ibid.*, **88**, 5363 (1966); (c) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, and W. D. Closson, *ibid.*, **89**, 5311 (1967).

(5) E. E. van Tamelen, G. Boche, and R. Greeley, *ibid.*, 90, 1677 (1968).

(6) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3990 (1966).

(7) A 1-ml sample of the radical anion solution is quenched in 5 ml of water containing 0.5 ml of benzene. A sample of the benzene layer is then analyzed by gas chromatography (4-ft Carbowax 20M at 140°) for dihydronaphthalenes and naphthalene. Since it is known that 1 mol of sodium naphthalene produces 0.5 mol of dihydronaphthalene, the amount of dihydronaphthalene is then one-half the concentration of the radical anion.

(8) The residual gases were H_2 and D_2. Entirely analogous results were obtained by Wender, Friedel, and Orchin with sodium hydride and heavy water: I. Wender, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, 71, 1140 (1949).

Shelton Bank, Thomas A. Lois
Department of Chemistry
State University of New York at Albany, Albany, New York 12203

Received May 6, 1968

Studies on Lactams. X.[1] Total Synthesis of 5,6-*trans*-Penicillin V Methyl Ester

Sir:

Intensive cooperative research in the United Kingdom and the United States during World War II led to the unequivocal determination of the structure and stereochemistry of penicillin,[2] but it was not until 1957 that an elegant total synthesis[3] of the antibiotic was achieved.

---

(1) (a) Presented before the 5th International Symposium on the Chemistry of Natural Products, London, July 1968. (b) For part IX, see A. K. Bose, G. Spiegelman, and M. S. Manhas, *Chem. Commun.*, 321 (1968).

(2) H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(3) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, 79, 1262 (1957); **81**, 3089, 5838 (1959).