mation of an organometallic halide.[37-40] The different stereochemical results are understandable if it is recalled that the halide ion is a much better leaving group than the alkoxide ion in the absence of acid. With the halometallic halide the analogs of reaction 8 proceed fast enough to exclude stereochemical rearrangement at the carbon–metal bond. With the alkoxymetallic halides, however, the elimination is slower, giving the carbon–metal bond time to lose its stereochemical identity. Most organometallic compounds probably lose their stereochemical identity with great ease, although they are capable of retaining it for very short periods of time or at very low temperatures.[41]

Experimental[42]

Materials.—Standard acids, buffers and solvents were prepared as before.[2,43] Compound I was prepared by the method of Romeyn and Wright,[44] and had m.p. 81.5–82.0°. Compound II was prepared in 50% yield from the corresponding chloromercurial. β-2-Methoxycyclohexylmercuric chloride (1.8 g., 0.0051 mole) was dissolved in 50 ml. of methanol and treated with 50 ml. of 0.10 *M* NaI in water. The resulting precipitate was filtered off, redissolved in 50 ml. of methanol, and the procedure repeated. The product was recrystallized from a 50% aqueous methanol solution, to obtain 1.1 g. of II, m.p. 95–96°. The melting point of II was unchanged on resolidification and remelting. β-2-Methoxycyclohexylmercuric chloride was prepared from the α-isomer in 12% yield by the "benzoyl peroxide" method of Romeyn and Wright.[44] It had a m.p. of 111–112° and a mixed m.p. with the α-isomer of 90–105°. The infrared spectra of I, the α-chloromercurial, and the β-chloromercurial in carbon tetrachloride are very similar, and are what would be expected of aliphatic ethers.

Kinetic Procedures.—Kinetic procedures for reactions carried out at 25° already have been described.[2] At other temperatures the reaction mixture was held at constant temperature in a thermostat of conventional design[2] and the optical density of periodically withdrawn samples was measured. The sort of data obtained by the second method is illustrated in Fig. 3.

Products.—The ultraviolet spectra of reaction mixtures from both I and II were determined on a Beckman DU spectrophotometer after the reactions were completed (after more than 10 half-lives had passed). The spectra were essentially identical with those expected if each mole of substrate yielded one-half mole of mercuric iodide.[2]

To identify other products, 0.50 g. of substrate was treated with 50 ml. of 11.86 *M* perchloric acid. After five minutes of stirring, 50 ml. of water was added with constant cooling and stirring. A solution of 40 g. of KOH in 100 ml. of water then was added, again accompanied by stirring and ice cooling to prevent overheating. A large precipitate of potassium perchlorate appeared during the addition of base and was filtered off; 50 ml. of water then was distilled out of the filtrate. This water was thoroughly extracted with 1 ml. of carbon tetrachloride. The carbon tetrachloride layer was separated, dried over anhydrous calcium sulfate, and its infrared spectrum determined by means of a Perkin-Elmer Infracord. For both I and II the resulting spectrum was essentially identical with that of a solution of methanol in carbon tetrachloride. The failure to observe cyclohexene may be due to hydration and/or polymerization, or the fact that it has a less intense spectrum than methanol.

Acknowledgment.—The authors are pleased to acknowledge the financial support of the National Science Foundation through grant No. N.S.F.-G5434 during part of the period when this work was in progress.

MINNEAPOLIS 14, MINN.

(37) D. R. James, R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).

(38) L. C. Swallen and C. E. Boord, THIS JOURNAL, **52**, 651 (1930).

(39) R. Paul, *Bull. soc. chim. France*, [4] **53**, 421 (1933).

(40) M. Tallman, THIS JOURNAL, **56**, 129 (1934).

(41) R. L. Letsinger, *ibid.*, **72**, 4842 (1950).

(42) All melting points are corrected.

(43) Maurice M. Kreevoy, THIS JOURNAL, **81**, 1099 (1958).

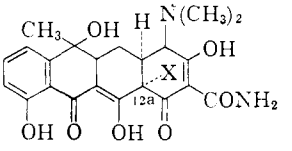
(44) J. Romeyn and G. F. Wright, *ibid.*, **69**, 697 (1947).

COMMUNICATIONS TO THE EDITOR

SOME TRANSFORMATIONS AT THE 12a-POSITION OF THE TETRACYCLINES

Sir:

Recent publications[1-3] concerning transformations at the 12a-position in the tetracycline series prompt us to report certain of our own results in this area.



I, X = OH
II, X = OCHO

Treatment of tetracycline (I) in pyridine with acetoformic acid reagent[4] in the cold yields O^{12a}-*formyltetracycline* (II) [m.p., 163° (dec.); ultraviolet spectrum[5] (solution preacidified to avoid rapid solvolysis), λ_{max} 267 and 360 mμ, log ε 4.29 and 4.07; infrared peak (KBr pellet), 5.84 μ: *Anal.* Found for $C_{23}H_{24}N_2O_9$: C, 58.12; H, 5.30; N, 6.10; CHO, 4.6]. O^{12a}-Formyltetracycline shows essentially the same antimicrobial activity *in vitro* and *in vivo* as tetracycline.[6] By following the rate of change of ultraviolet absorption of II in aqueous buffers, approximate half-lives for hydrolysis to tetracycline at *p*H 2.0, 4.0, 6.0 and 7.5 were indicated to be 6 hours, 4 hours, 30 minutes and 5 minutes, respectively.

Refluxing O^{12a}-formyltetracycline in toluene yields formic acid (presumably *via cis*-elimination) and *4a,12a-anhydrotetracycline* (III). [Ultraviolet spectrum[5] (after 30 minutes to achieve tautomeric equilibrium): λ_{max} 247, 329, 405 and 426 mμ, log ε 4.29, 3.82, 4.33, 4.35. *Anal.* Found for

(1) H. Muxfeldt and A. Kreutzer, *Naturwissenshaften*, **46**, 204 (1959).

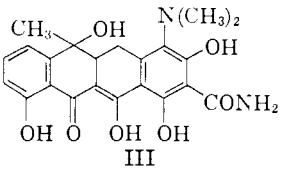
(2) C. E. Holmlund, W. W. Andres and A. J. Shay, THIS JOURNAL, **81**, 4748 and 4750 (1959).

(3) Belgian Patent 572,382. We have been advised that a paper by Drs. A. Green and J. H. Booth describing substance IV is in press in THIS JOURNAL.

(4) A mixture of acetic–formic anhydride and acetic acid, *cf.* V. C. Mehlenbacher in "Organic Analyses," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 37.

(5) Solvent was methanol, 0.01 *N* in hydrochloric acid.

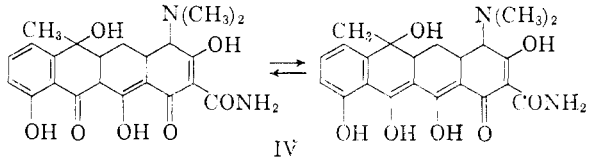
(6) We are indebted to Drs. A. R. English and T. J. McBride for antimicrobial investigations.



III

$C_{22}H_{22}N_2O_7$: C, 61.83; H, 5.29; N, 6.50]. Mild acid degradation converts III, *via* 5a,6-*trans* elimination of water, to terrarubein,[7] the only common tetracycline-oxytetracycline degradation product reported to date.

Catalytic hydrogenation [Pd/C in tetrahydrofuran] of O^{12a}-formyltetracycline yields 12a-deoxytetracycline (IV), a compound which Green and



IV

Booth have prepared independently *via* a zinc in ammonium hydroxide reduction of tetracycline.[2,3] Compound IV retains appreciable antimicrobial activity.[6] Reoxidation of IV to tetracycline has been reported.[2] Acid degradation converts IV to *5a,6-anhydro-12a-deoxytetracycline* [ultraviolet spectrum[5]: λ_{max} 272, 325, 378 and 434 mμ, log ϵ 4.52, 3.95, 4.12 and 4.34. *Anal.* Found for $C_{22}H_{22}N_2O_6 \cdot HCl$: C, 59.5; H, 5.37; N, 6.14].

Transformations similar to those described above also have been carried out on other members of the tetracycline series.

(7) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

CHEMICAL RESEARCH AND DEVELOPMENT DEPARTMENT
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RECEIVED NOVEMBER 30, 1959

HYDROBORATION AS A CONVENIENT SYNTHETIC ROUTE TO THE ALIPHATIC BORONIC AND BORINIC ACIDS AND ESTERS

Sir:

The aliphatic boronic acids are generally synthesized by the reaction of the Grignard reagent with methyl borate at $-70°$.[1] The related borinic acids have been obtained from trialkylboranes by hydrolysis of the initial oxidation product[2] or by hydrolysis of the dialkylboron halide[3] also derived from the trialkylborane.[3,4] The discovery that olefins rapidly undergo hydroboration to form the corresponding organoboranes in essentially quantitative yield[5] led us to explore synthetic routes to the aliphatic boronic and borinic acids based on the hydroboration reaction.

(1) H. R. Snyder, J. A. Kuck and J. R. Johnson, THIS JOURNAL, **60**, 105 (1938).

(2) J. R. Johnson and M. G. Van Campen, Jr., *ibid.*, **60**, 121 (1938).

(3) J. R. Johnson, H. R. Snyder and M. G. Van Campen, Jr., *ibid.*, **60**, 115 (1938).

(4) P. A. McCusker, G. F. Hennion and E. C. Ashby, *ibid.*, **79**, 5192 (1957).

(5) H. C. Brown and B. C. Subba Rao, *ibid.*, **78**, 5694 (1956); H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1137 (1957); H. C. Brown and G. Zweifel, THIS JOURNAL, **81**, 4106 (1959).

Cyclopentene, 0.300 mole, was added over 1 hr. to a solution of 0.150 mole of diborane in 350 ml. of tetrahydrofuran at 0°. After a second hour at 0°, 100 ml. of methanol was added and the mixture was distilled. There was obtained 17.4 g. (65% yield) of methyl dicyclopentaneborinate, b.p. 121–122° at 21 mm., $n^{20}D$ 1.4717.

Anal. Calcd. for $C_{11}H_{21}BO$: C, 73.35; H, 11.75; B, 6.01. Found: C, 73.01; H, 11.55; B, 6.00.

Similarly, 1-pentene was converted into methyl di-1-pentaneborinate, 16.3 g. (60% yield), b.p. 101–104 at 20 mm., $n^{20}D$ 1.4238.

Anal. Calcd. for $C_{11}H_{25}BO$: C, 71.75; H, 13.69; B, 5.88. Found: C, 71.54; H, 13.64; B, 5.87.

Addition of 0.150 mole of diborane to 0.300 mole of the olefin in tetrahydrofuran results in the predominant formation of the trialkylborane. However, redistribution[6] occurs at 25–50° to form the monoalkylborane in reasonable yield.

Diborane, 0.150 mole, was passed into a solution of 20.4 g., 0.300 mole, of cyclopentene in 200 ml. of tetrahydrofuran at 0°. The reaction mixture then was maintained at 50° for 24 hr. To the cooled reaction mixture 100 ml. of methanol was added and the reaction mixture was distilled. There was obtained 25.4 g. (60% yield) of dimethyl cyclopentaneboronate, b.p. 60–62° at 20 mm., $n^{20}D$ 1.4300.

Similarly, 1-pentene was converted into dimethyl 1-pentaneboronate, 19.1 g., (44% yield), b.p. 55–57° at 20 mm., $n^{20}D$ 1.4025.

Anal. Calcd. for $C_7H_{17}BO_2$: C, 58.37; H, 11.90; B, 7.51. Found: C, 58.34; H, 11.80; B, 7.50.

Treatment of the 1-butane- and 1-hexaneboronic acids with ammoniacal silver nitrate converts them into *n*-octane and *n*-dodecane in excellent yield.[1] Consequently, the conversion of unsaturated compounds into the corresponding boronic acid and then treatment with ammonical silver nitrate should provide a useful dimerization procedure for alkenes and certain of their functional derivatives: $2RCH{=}CH_2 \rightarrow (RCH_2CH_2)_2$. We are exploring the full scope and utility of this synthesis.

(6) H. I. Schlesinger and A. O. Walker, *ibid.*, **57**, 621 (1935).

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RECEIVED DECEMBER 31, 1959

Δ^4-3-KETO STEROIDAL ENOL ETHERS. PARADOXICAL DEPENDENCY OF THEIR EFFECTIVENESS ON THE ADMINISTRATION ROUTE

Sir:

We have found that through enol etherification with suitable alcohols the hormonal activity of Δ^4-3-keto steroids can be lessened by parenteral and enhanced by oral use. Of the many enol ethers we have assayed,[1] several were undescribed:

(1) Biological and cancer chemotherapy tests performed in our laboratories with the collaboration of G. Bruni, F. Galletti, G. Falconi and A. Meli. The compounds were mostly administered in oily solution both by parenteral and oral route. The absence of parent ketones