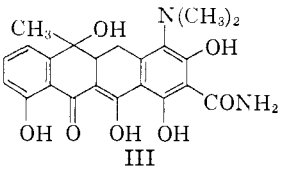
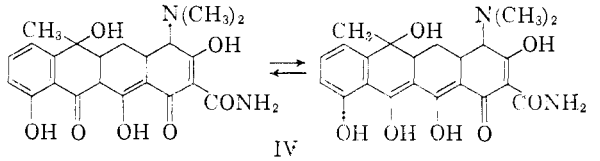


III

$C_{22}H_{22}N_2O_7$: 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).

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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

of androstenedione (I): isopropyl, m.p. 151–153° (all m.p.s. uncorr.), $[\alpha]_D$ −88° (all rotns. in dioxane)[2]; allyl, m.p. 142–144°, $[\alpha]_D$ −85.5°; *n*-butyl, m.p. 140–144°, $[\alpha]_D$ −79°; isobutyl, m.p. 144–147°, $[\alpha]_D$ −77.5°; *sec*-butyl), with m.p. 132–134.5°, $[\alpha]_D$ −81°; *n*-amyl, m.p. 104–106°, $[\alpha]_D$ −76°; isoamyl, m.p. 113–115°, $[\alpha]_D$ −71.5°; *n*-hexyl, m.p. 85–87°, $[\alpha]_D$ −73°; (2-methyl)-pentyl, m.p. 87–90°, $[\alpha]_D$ −69°; (4-methyl)-pentyl, m.p. 119–121°, $[\alpha]_D$ −67°; (2-ethyl)-butyl, m.p. 83–85°, $[\alpha]_D$ −65.6°; (1,3-dimethyl)-butyl, m.p. 122–124°, $[\alpha]_D$ −84°; *n*-heptyl, m.p. 66–67°, $[\alpha]_D$ −71°; *n*-octyl, m.p. 65–66°; $[\alpha]_D$ −63°; *n*-decyl, m.p. 45–47°, $[\alpha]_D$ −37.5°; (2-chloro)-ethyl, m.p. 135–138°, $[\alpha]_D$ −75°; (4-chloro)-butyl, m.p. 108–111°, $[\alpha]_D$ −66°; cyclopentyl, m.p. 181–183°, $[\alpha]_D$ −88.5°; furfuryl, m.p. 182–183°, $[\alpha]_D$ −83°; (3-cyclopentyl)-propyl, m.p. 105–107°, $[\alpha]_D$ −75°; phenyl, m.p. 140–143°, $[\alpha]_D$ −67°; cinnamyl, m.p. 136–137°, $[\alpha]_D$ −70°; of testosterone (II): isopropyl, m.p. 118–121°, $[\alpha]_D$ −137°[3]; *n*-butyl, m.p. 93–96°, $[\alpha]_D$ −123.5°; isobutyl, m.p. 118–120°, $[\alpha]_D$ −122°; *sec*-butyl, with m.p. 109–112°, $[\alpha]_D$ −133.5°; *n*-amyl, m.p. 104–106°, $[\alpha]_D$ −120°; isoamyl, m.p. 107–109°, $[\alpha]_D$ −117°; *n*-hexyl, m.p. 109–112°, $[\alpha]_D$ −114°; (2-methyl)-pentyl, m.p. 106–109.5°, $[\alpha]_D$ −115°; *n*-heptyl, m.p. 89–91°, $[\alpha]_D$ − 111°; *n*-octyl, m.p. 78–79°, $[\alpha]_D$ −111°; *n*-decyl, m.p. 71–73°, $[\alpha]_D$ −105°; of (II) formate: ethyl, m.p. 127–130°, $[\alpha]_D$ −133°; cyclohexyl, m.p. 133–137.5°, $[\alpha]_D$ −149°; of (II) acetate: *n*-heptyl, m.p. 127.5–129°, $[\alpha]_D$ −120°; (carboethoxy)-methyl, m.p. 120–121°, $[\alpha]_D$ −120°; (1-carboethoxy)-ethyl, m.p. 156–159°; $[\alpha]_D$ −73°; of (II) propionate: the *sec*-butyl, m.p. 130–132°, $[\alpha]_D$ −130°; *tert*-amyl, with m.p. 122–125°, $[\alpha]_D$ −120°; *n*-hexyl, m.p. 110–112°, $[\alpha]_D$ −115°; (2-ethyl)-butyl, m.p. 102–104°, $[\alpha]_D$ −120°; (2-chloro)-ethyl, m.p. 148–150°, $[\alpha]_D$ −125°; carbomethoxy-methyl, m.p. 103–105°, $[\alpha]_D$ −121°; cyclohexyl, m.p. 140–143°, $[\alpha]_D$ −123°; phenyl, m.p. 101–103°, $[\alpha]_D$ −132°; of (II) valerate: cyclohexyl, m.p. 127–129°, $[\alpha]_D$ −117°; of (II) enanthate: ethyl, m.p. 90–91°, $[\alpha]_D$ −113°; *n*-hexyl, m.p. 71.5–72.5°, $[\alpha]_D$ −96°; *n*-heptyl, m.p. 64–66°, $[\alpha]_D$ −95°; cyclohexyl, m.p. 111–113°, $[\alpha]_D$–104°; *m*-nitrobenzyl, m.p. 119.5–120.5°, $[\alpha]_D$ −73°; of (II) undecylenate: benzyl, m.p. 113–114°, $[\alpha]_D$ −87.5°; of (II) phenylpropionate: *n*-hexyl, m.p. 85–86°, $[\alpha]_D$ −89°; cyclohexyl, m.p. 135–136°, $[\alpha]_D$ −92.5°; of methyltestosterone (III): *n*-butyl, m.p. 102–104°, $[\alpha]_D$ −146°[3]; isobutyl, m.p. 128–130°, $[\alpha]_D$ −139°; *sec*-butyl, with m.p. 131–134°, $[\alpha]_D$ −145°; *n*-amyl, m.p. 96–98°, $[\alpha]_D$ −134.5°; isoamyl, m.p. 121–125°, $[\alpha]_D$ −134°; *n*-hexyl, m.p. 79–81°, $[\alpha]_D$ −131°; (4-methyl)-pentyl, m.p. 102–103°, $[\alpha]_D$ − 134°; (2-methyl)-pentyl, m.p. 85–89°, $[\alpha]_D$ −120°; (2-ethyl)-butyl, m.p. 106–107°, $[\alpha]_D$ −129.5°; (1,3-dimethyl)-butyl, m.p. 113–115°, $[\alpha]_D$ −135°; *n*-heptyl, m.p. 62–64°, $[\alpha]_D$ −123.5°; *n*-octyl, m.p. 35–41°, $[\alpha]_D$ −109°; (4-chloro)-butyl, m.p. 90–93°, $[\alpha]_D$ −110°; cyclopentyl, m.p. 148–152°, $[\alpha]_D$ −150°; cyclohexyl, m.p. 142–144°, $[\alpha]_D$ −136°; benzyl, m.p. 132–135°, $[\alpha]_D$ −128°; phenyl, m.p. 149–151°, $[\alpha]_D$ −140°; of (III) acetate: ethyl, m.p. 132–133°, $[\alpha]_D$ −123°; of 19-nortestosterone (IV) acetate: ethyl, m.p. 131–134°, $[\alpha]_D$ −165°; *n*-butyl, m.p. 128.5–131°, $[\alpha]_D$ −136.5°; *n*-amyl, m.p. 75.5–78°, $[\alpha]_D$ −140°; *n*-heptyl, m.p. 64.5–65.5°, $[\alpha]_D$ −135.5°; of (IV) propionate: ethyl, m.p. 116–118°, $[\alpha]_D$ −155°; cyclohexyl, m.p. 124–126°, $[\alpha]_D$ −135°; benzyl, m.p. 174–176°, $[\alpha]_D$ −132°; of cortisone (V): ethyl, m.p. 185–187°, $[\alpha]_D$ −25°; *n*-amyl, m.p. 149–152°, $[\alpha]_D$ −18.2°; *n*-hexyl, m.p. 139–141°, $[\alpha]_D$ − 18.4°; *n*-heptyl, m.p. 131–135°, $[\alpha]_D$ −17.5°; of (V) acetate: methyl, m.p. 189–192°, $[\alpha]_D$ +20.5°; propyl, m.p. 179–183, $[\alpha]_D$ +20.9°; isopropyl, m.p. 187–191°, $[\alpha]_D$ +22.8°; *n*-butyl, m.p. 152–155°, $[\alpha]_D$ + 17.8°; *sec*-butyl, with m.p. 188–192°, $[\alpha]_D$ +20°; *n*-amyl, m.p. 151–153.5°, $[\alpha]_D$ + 17.7°; *n*-hexyl, m.p. 143–144°, $[\alpha]_D$ +19°; *n*-heptyl, m.p. 141.5–143.5°, $[\alpha]_D$ +17°; *n*-octyl, m.p. 162.5–164°, $[\alpha]_D$ +19°; of (V) enanthate: *n*-hexyl, m.p. 105–107°, $[\alpha]_D$ +2°; of hydrocortisone (VI): ethyl, m.p. 193–195°, $[\alpha]_D$ −70°; propyl, m.p. 174–175.5°, $[\alpha]_D$ −63°; of (VI) acetate: ethyl, m.p. 156–158.5, $[\alpha]_D$ −27°; of progesterone (VII): ethyl, m.p. 106–107°, $[\alpha]_D$ −47°; *n*-butyl, m.p. 70–71°, $[\alpha]_D$ −43°; *n*-amyl, m.p. 66.5–68°, $[\alpha]_D$ −49°; *n*-heptyl, m.p. 61–63°, $[\alpha]_D$ −44°; cyclopentyl, m.p. 105–106°, $[\alpha]_D$ −47.5°; cyclohexyl, m.p. 115–116.5°, $[\alpha]_D$ −52.5°; of 17α-acetoxyprogesterone (VIII): *n*-amyl, m.p. 125–126°, $[\alpha]_D$ −126.5°; *n*-heptyl, m.p. 59–62°, $[\alpha]_D$ −124°; cyclopentyl, m.p. 137–138°, $[\alpha]_D$ −147°.

Confirming previous findings,[4] the I and II derivatives revealed subcutaneously no appreciable androgenic and myotrophic activity[5] (while many representatives retained anti-mammary cancer action both experimentally[1] and clinically[6]). The peculiar hormonal activities of parent ketones are still observable, but in a reduced degree, in the enol ethers of III, IV, V, VI, VII, and VIII, always administered subcutaneously.[7] Most surprising, however, was the marked enhancement of activity exhibited by the same ethers (from III to VIII) given orally. By this route, *e.g.*, cyclohexyl enol ether of III is more than five times as potent as III both as an androgen and a myotrophic agent,[5] thus duplicating the effect of an equal dose of testosterone propionate given parenterally.[8] The propyl derivative of V acetate exhibits about the same antiinflammatory effect as prednisone.[8,9] The cyclopentyl derivative of VII appears to be ten

was checked according to M. Bianchi, *La Chimica e l'Industria*, **41**, 33 (1959).

(2) All compounds gave satisfactory results upon elemental analysis and showed the characteristic ultraviolet and infrared absorption spectra.

(3) Most compounds of this group give adducts frequently during crystallization.

(4) A. Ercoli, *Naturwiss.*, **45**, 576 (1958); A. Ercoli, *Boll. Soc. Ital. Biol. Sper.*, **34**, 1722 (1958).

(5) Seven-day castrate male rat assay.

(6) G. F. Gardini, *Giorn. Ital. Chemioterap.*, **3**, 408 (1956); C. Monetti and F. Mainoldi, in press.

(7) With a marked improvement of anabolic-androgenic ratios for the IV derivatives.

(8) Results also clinically confirmed.

(9) Agar pellet granuloma test.

times as potent as VII in the Clauberg test without eliciting the narcotic effect of the latter. The oral activity generally decreases by more than seven - membered straight chains. Comparable findings on enol ethers of the above cited ketones variously substituted soon will be reported elsewhere.

These novel compounds were obtained: (A) with orthoformic esters in the conventional manner[10]; (B) by treating Δ^4-3-ketones and alcohols with isoöctane as azeotropic carrier[11]; (C) by acid-catalyzed interchange reaction[12] between the chosen alcohol and a preformed (mostly ethyl) enol ether generally obtained with (A) procedure; (D) by the same way without isolation of firstly formed ether; (E) by converting in proper conditions the as above obtained enol ethers to the desired compounds by reduction, acylation, saponification or condensation reactions.

(10) A. Serini and H. Köster, *Ber.*, **71**, 1766 (1938).

(11) A. Ercoli and P. de Ruggieri, U. S. Patent 2,835,667 (May 20, 1958). Senior author wishes to thank Dr. P. de Ruggieri (Ormonoterapia Richter, Milano) for his effective collaboration in developing method B.

(12) A. Ercoli, German Patent 1,068,256 (published November 5, 1959).

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RECEIVED DECEMBER 21, 1959

THE PREPARATION OF *t*-BUTYLDIALKYLBORANES AND 1-*t*-BUTYLBOROCYCLOPENTANE FROM OLEFINS AND TRIMETHYLAMINE *t*-BUTYLBORANE

Sir:

Recent interest in the preparation of mixed trialkylboranes[1,2] and 1-alkylborocyclopentanes[3] prompts us to report a new method for the preparation of these compounds.

Trimethylamine *t*-butylborane,[4] which is prepared by the lithium aluminum hydride reduction of *t*-butylboroxine in the presence of trimethylamine, has been found to add to olefins at 50–60° at an extremely rapid rate. The great rates of these reactions are in sharp contrast to those observed with pyridine borane[5] and trimethylamine borane[6] since the latter reactions required higher temperatures and longer reaction times. This rate difference is attributed to the greater rate of dissociation of the *t*-butylborane amine complex.

The addition of ethylene, propylene, 1-butene and *i*-butene to 0.10 mole quantities of trimethyl amine *t*-butylborane at atmospheric pressure and 50–60° was complete after 1–2 hours. Trimethylamine was evolved during the reaction. Vacuum distillation of the products afforded the corresponding *t*-butyl dialkylboranes in up to 90% yield. Similar treatment of 1,3-butadiene and isoprene afforded 1-*t*-butyl borocyclopentane and 1-*t*-butyl-3-methylborocyclopentane, respectively. Structures were assigned on the basis of C, H and B analyses, infrared spectra and H^1n.m.r. spectra.

(1) G. F. Hennion, P. A. McCusker and A. J. Rutkowski, THIS JOURNAL, **80**, 617 (1958).

(2) A. G. Davies, D. G. Hare and R. F. M. White, *Chem. Ind.*, 1315 (1959).

(3) R. Koster, *Angew. Chem.*, 520 (1959).

(4) M. F. Hawthorne, THIS JOURNAL, **81**, 5836 (1959).

(5) M. F. Hawthorne, *J. Org. Chem.*, **23**, 1788 (1958).

(6) E. C. Ashby, THIS JOURNAL, **81**, 4791 (1959).

The *t*-butyl-di-isobutylborane obtained in this work gave a H^1n.m.r. spectrum identical to that obtained by Davies, *et al.*,[2] with the exception of the absence of the small band which these authors attributed to restricted rotation.

Dimethyldivinylsilane reacted smoothly with trimethylamine *t*-butylborane to produce 1-boro-1-*t*-butyl-4,4-dimethyl-4-silacyclohexane, a novel heterocycle which contains a boron atom and a silicon atom in a six-membered ring. The table records representative data.

CHARACTERISTICS OF MIXED BORANES

Borane	B.p. °C. (mm.)	Yield, %
t-Butyl diethyl	60 (70)	35
t-Butyl di-(1-propyl)	67 (22)	88
t-Butyl di-(1-butyl)	74 (6.1)	90
t-Butyl di-(*i*-butyl)	62 (7.5)	85
1-*t*-Butyl borocyclopentane	55 (55)	60
1-*t*-Butyl-3-methyl borocylopentane	67 (54)	55
1-Boro-1-*t*-butyl-4,4-dimethyl-4-silacyclohexane	44 (2)	58

Further work with other trimethylamine alkylborane reactions is in progress and will be reported at a later date.

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RECEIVED DECEMBER 17, 1959

A SIMPLE PREPARATION OF DIALKYL ALKYLTHIOBORONATES AND TRIALKYLTHIOBORATES

Sir:

Trimethylamine alkylboranes, prepared from the corresponding alkylboroxines by lithium aluminum hydride reduction in the presence of trimethylamine,[1] and alkylthiols react at 60–100° to produce the corresponding dialkyl alkylthioboronates in moderate yields.

$$RB^-H_2—N^+(CH_3)_3 + 2R'SH \longrightarrow 2H_2 + N(CH_3)_3 + RB(SR')_2$$

The use of trimethylamine borane with high boiling thiols affords the corresponding trialkylthioborates. Both types of reaction appear to be general and constitute simple routes to previously unavailable compounds.

Dialkyl alkylthioboronates and trialkylthioborates are hydrolyzed easily by water to the corresponding thiol, alkylboronic acid and boric acid, respectively. The dialkyl alkylthioboronates did not disproportionate appreciably during distillation at temperatures up to 150°. The table presents representative data. Analytical values obtained for C, H and B were satisfactory.

Treatment of di-*n*-amyl-*n*-butyl thioboronate and the corresponding *t*-butyl compound with excess mercuric chloride in toluene at 80° produced the corresponding alkyl boron dichlorides in 60% yield. The formation of the Hg–S bond may provide driving-force for other similar reactions.

$$RB(SR')_2 + 2\ HgCl_2 \longrightarrow RBCl_2 + 2\ ClHgSR'$$

Further work is in progress and will be reported at a later date.

(1) M. F. Hawthorne, THIS JOURNAL, **81**, 5836 (1959).