Attempted Dibenzoylation of Biuret

To a suspension of 0.50 mole of sodium hydride in 250 ml of refluxing DME was added a solution of 5.16 g (0.05 mole) of biuret and 17.02 g (0.125 mole) of methyl benzoate in 150 ml of DME. The reaction mixture was refluxed for 19.5 h and then processed in the usual manner to afford, after one recrystallization from absolute ethanol, 5.10 g (38%) of 1,3-dibenzoylurea (**1***a*), m.p. 215–217°; mixture m.p. 215–217°. The i.r. spectrum of this material was identical with that of a sample of **1***a* prepared from the dibenzoylation of urea.

1. J. F. Wolfe and G. B. Trimitsis. J. Org. Chem. **33**, 894 (1968).
2. J. F. Wolfe, G. B. Trimitsis, and C. R. Hauser. Can. J. Chem. **46**, 2561 (1968).
3. E. Schmidt. J. prakt. Chem. [2], **5**, 58 (1872).
4. A. F. Holleman. Chem. Ber. **23**, 3000 (1890).
5. O. C. Billeter. Chem. Ber. **36**, 3218 (1903).
6. R. A. Jacobsen. U.S. Patent 2,090,593 (1937); Chem. Abst. **31**, 7068 (1937).
7. A. E. Dixon. J. Chem. Soc. **75**, 383 (1899).

Selective reduction of esters with sodium trimethoxyborohydride

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The rate of reduction of representative methyl esters with sodium trimethoxyborohydride decreases in the order primary > secondary > tertiary. Sodium trimethoxyborohydride reduces with 100% selectivity the secondary ester group in the alicyclic diester–acid **2***c*.

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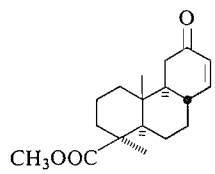
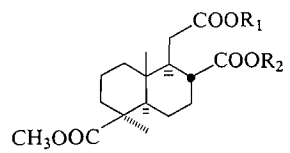
Since its first preparation and brief examination of its properties in 1953 by Brown and Mead (1), sodium trimethoxyborohydride appears to have received little attention by organic chemists (2). We now report the 100% selective reduction of the alicyclic diester–acid **2***c* with sodium trimethoxyborohydride in refluxing dimethoxyethane. In order to gauge the synthetic utility of this reagent in selective ester reductions, we have measured the rates of reduction of the primary, secondary, and tertiary methyl esters, methyl 3-phenylpropionate, methyl cyclohexylcarboxylate, and methyl abietate **4**.

The diester–acid **2***c* was prepared from the known compound (3) methyl 12-oxopodocarp-13-en-16-oate **1**. Ozonolysis of **1** in ethyl acetate at 0°, followed by treatment with hydrogen peroxide in acetic acid yielded a dicarboxylic acid **2***a*, which on methylation with diazomethane afforded the triester **2***b*. Selective hydrolysis with one mole-equivalent of sodium hydroxide in methanol (4) yielded the diester–acid **2***c* in 75% overall yield from **1**.

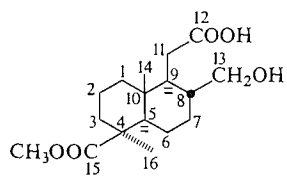
The selective reduction of the secondary ester function in **2***c* was accomplished by treatment with a three mole-equivalent excess of sodium trimethoxyborohydride in refluxing dimethoxyethane. The ester – acid – alcohol **3** was obtained in greater than 95% yield, either as the free alcohol or in the form of its δ-lactone. Careful examination of the crude reaction product by proton magnetic resonance (p.m.r.) spectroscopy showed that the C-15 carbomethoxy group at 3.64 p.p.m. had suffered no observable reduction. The



1



2 *a*, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = H$; $R_2 = CH_3$



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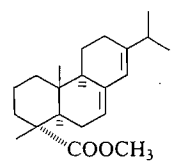

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TABLE I

Reduction of esters by sodium trimethoxyborohydride*

Ester	Time for 50% reduction (min)	Time for 100% reduction (min)	Product
Methyl 3-phenylpropionate	17	40	3-Phenylpropanol
Methyl cyclohexylcarboxylate	27	60	Cyclohexylcarbinol
Diester–acid **2***c*	32	75	**3**
Methyl abietate **4**	255	600	Abietenol

*3 mole-equivalents excess in refluxing dimethoxyethane at 83°.

carboxyl function at C-12 was likewise completely unaffected as demonstrated by quantitative lactone formation.

To examine the general utility of sodium trimethoxyborohydride in dimethoxyethane in ester reductions, the rates of reaction of the esters, methyl 3-phenylpropionate, methyl cyclohexylcarboxylate, and methyl abietate were measured using the same procedure as above with three mole-equivalents excess of the reagent. Reduction times and products are summarized in Table I. The expected alcohols were all produced in essentially quantitative yield and were characterized by their p.m.r. spectra and as their 3,5-dinitrobenzoate derivatives.

Since sodium trimethoxyborohydride does not react with the carboxyl group (1, 2) (except to form the carboxylate anion) it would seem that the selective reduction of ester groups in the presence of carboxylic acids is readily achieved with this reagent. The relative rates of reduction of the primary and secondary esters methyl 3-phenylpropionate and methyl cyclohexanecarboxylate (1.6:1 respectively for 50% reduction) show that some selectivity (ca. 60%) may be achieved between them (5). This selectivity could probably be improved considerably by operating at lower temperatures, for example 0°. The very slow rate of reduction of the tertiary ester, methyl abietate, indicates that excellent selectivity can be achieved between primary and secondary esters in the presence of tertiary esters and that the reagent should be of synthetic use in these areas. The total non-reaction of the axial C-15 methyl ester in the diester–acid **2***c* arises because of the severe 1,3 diaxial interaction with the C-14 methyl group. This behavior may be compared with the more normal behavior of the tertiary, equatorial C-18 methyl ester in methyl abietate which, although slow, does undergo reduction.

Sodium borohydride in large excess in methanol (6) reduces aromatic carboxylic esters to alcohols in good yields, but results with aliphatic and alicyclic esters were less satisfactory. Lithium borohydride on the other hand reduces esters well, but also attacks carboxylic acids to varying extents (2, 7) so that selective reduction of esters in the presence of acids is rarely possible. It is likely that sodium trimethoxyborohydride, despite its reactivity, is more sensitive to the steric environment of the substrate than the tetrahydro reagents. Thus, like lithium tritertiarybutoxyaluminium hydride (8) it exhibits a wide range of relative reduction rates in its reaction with esters. A variety of selective reductions amongst different functional groups can be readily carried out with alkoxyaluminohydrides (8, 9). Lithium diethoxyaluminohydride has been reported to show some selectivity in the reduction of simple esters (10). However, on currently available evidence it would appear that sodium trimethoxyborohydride is the preferred reagent for achieving reasonable selectivity in ester reductions.

In view of Brown's report (1) that sodium trimethoxyborohydride reacted only slowly with esters in ethyl ether at reflux or in *n*-butyl ether at 110–140°, we are at present investigating the possibility of a specific solvent effect by dimethoxyethane. In addition, we are examining the effects of different alcohol moieties in the ester group with a view to further improving the selectivity between primary and secondary esters.

Experimental

Melting points are uncorrected and were determined on a Köfler hot-stage apparatus. Infrared spectra were recorded in chloroform. Proton magnetic resonance (p.m.r.) spectra were determined on Varian Associates HA-100 and A-60 spectrometers in deuteriochloroform with TMS as internal standard. Mass spectra were obtained on a Hitachi Perkin–Elmer RMU-6A spectrom-

eter. Carbon and hydrogen analyses were determined by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

The sodium trimethoxyborohydride used in these experiments was obtained from Alfa Inorganics Inc., Beverly, Massachusetts.

4α,10-Dimethyl-4β-carbomethoxy-8α-carboxy-decahydro-9-naphthaleneacetic Acid 2a

The α,β-unsaturated ketone **1** (3) (1.00 g (3.45 mmoles)) m.p. 124–126°, was dissolved in 25 ml of dry ethyl acetate and oxygen containing ca. 2% ozone (Welsbach T-408 ozonizer) was passed through the solution at 0° for 30 min. After removal of excess ozone with a stream of nitrogen the solvent was removed *in vacuo* at 40°. To the residue were added 30 ml of acetic acid, 20 ml of 30% hydrogen peroxide, and 10 drops of concentrated hydrochloric acid and the mixture stirred at room temperature overnight and then heated for 1.5 h on the steam bath. The product was taken up in benzene, washed thoroughly with water, then with three 50 ml portions of saturated sodium carbonate solution, and finally once with 50 ml of water. The combined alkaline washings were acidified to pH 1 with 2 *N* sulfuric acid and extracted with benzene. The washed and dried (anhydrous sodium sulfate) benzene extract was evaporated *in vacuo* to give 0.90 g (80%) of **2a** as an oil which crystallized slowly on standing. Recrystallization from hexane – ethyl acetate (4:1) gave the diacid as colorless needles m.p. 182–184°; i.r. ν_{max}, 3500–2500 (COOH), 1730–1700 cm^{-1} (>CO, $COOCH_3$ and COOH); p.m.r. δ, 0.66 (s, 3H, C-14 CH_3); 1.20 (s, 3H, C-16 CH_3); 3.66 (s, 3H, $COOCH_3$); 10.5–11.5 p.p.m. (broad, 2H, COOH).

Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.64; H, 8.11.

Methyl 4α,10-Dimethyl-14β,8α-dicarbomethoxy-decahydro-9-naphthalene-acetate 2b

Methylation of the diacid **2a** was carried out by the addition of a freshly prepared solution of diazomethane in ether to a stirred solution of 0.650 g (2 mmoles) of **2a** in ether–methanol at room temperature. Evaporation of the solvent *in vacuo* afforded 0.705 g (99–100%) of the crystalline triester **2b**. Recrystallization from hexane – ethyl acetate (9:1) yielded **2b** as colorless prisms m.p. 91.5–92.5°; i.r. ν_{max} 1740 (C-12 $COOCH_3$), 1735 (C-13 $COOCH_3$), 1725 (C-15 $COOCH_3$), 1220, and 1165 cm^{-1} (O—CH_3); p.m.r. δ, 0.59 (s, 3H, C-14 CH_3); 1.13 (s, 3H, C-16 CH_3), 3.53 (s, 3H, C-15 $COOCH_3$), 3.50 (s, 3H, C-13 $COOCH_3$), and 3.48 p.p.m. (s, 3H, C-12 $COOCH_3$); mol. wt. 354 (mass spectrum).

Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.44; H, 8.11.

4α,10-Dimethyl-4β,8α-dicarbomethoxy-decahydro-9-naphthaleneacetic Acid 2c

To a sample of 1.00 g (2.83 mmoles) of triester **2b** (m.p. 89–91°) dissolved in 32 ml of methanol were added 2.85 ml of 1 *N* sodium hydroxide and 57.0 ml water (making the total solution 0.05 *N* in sodium hydroxide). The mixture was refluxed with stirring under nitrogen for 3.5 h. After removal of the majority of methanol *in vacuo*, the aqueous residue was washed with ether (3 × 50 ml) and the ethereal washings counterwashed with 50 ml of water. The aqueous phases were then combined and acidified to pH 1 with 2 *N* sulfuric acid and extracted with benzene. The benzene layer was washed with water, dried with anhydrous sodium sulfate, and after evaporation *in vacuo* yielded 875 mg (91%) of **2c** as an oil which crystallized on standing. Recrystallization from hexane – ethyl acetate (9:1) gave **2c** as colorless plates m.p. 138–139°; i.r. ν_{max} 3600–2600 (COOH), 1735 ($COOCH_3$), 1715 (COOH), 1220 and 1165 cm^{-1} (O—CH_3, CH_2—O); p.m.r. δ, 0.63 (s, 3H, C-14 CH_3), 1.16 (s, 3H, C-16 CH_3), 3.57 (s, 3H, C-15 $COOCH_3$), 3.54 (s, 3H, C-13 $COOCH_3$), 11.32 p.p.m. (broad, 1H, COOH).

Anal. Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.54; H, 8.21.

Work-up of the neutral ether washings yielded 90 mg of crystalline unchanged starting material **2b**.

4α,10-Dimethyl-4β-carbomethoxy-8α-hydroxymethylene-decahydro-9-naphthaleneacetic Acid 3

A solution of 0.500 g (1.47 mmoles) of diester-acid **2c** in 50 ml dimethoxyethane (freshly distilled from calcium hydride) was added dropwise to 2.25 g (5.85 mmoles) of sodium trimethoxyborohydride in a 200 ml flask under a nitrogen atmosphere. After a short period of frothing and hydrogen evolution, the mixture was stirred and brought to reflux for 75 min. After cooling, the reaction mixture was poured into cold water, acidified with 2 *N* sulfuric acid and the liberated product extracted with benzene. The benzene extracts after washing with water, brine and drying (anhydrous sodium sulfate) afforded on evaporation *in vacuo* 0.45 g (98%) of crystalline hydroxy-acid **3**. However, recrystallization from hexane – ethyl acetate yielded colorless plates m.p. 136–137° which were found to be the δ-lactone of **3**. The impure crystalline **3** showed: i.r. ν_{max} 3600–2550 (COOH), 1730 ($COOCH_3$), 1720 cm^{-1} (COOH); p.m.r. δ, 0.68 (s, 3H, C-14 CH_3), 1.18 (s, 3H, C-16 CH_3), 3.64 (s, 3H, $COOCH_3$), 3.75 and 4.28 (m, 2H, AB part of an ABX, J_{AB} = 11 Hz, J_{BX} = 10 Hz, and J_{AX} = 5 Hz; C-13 CH_2), 8.70 p.p.m. (broad, 2H, COOH and OH). It was not possible to recrystallize **3** even from cold, nonpolar solvents without the loss of water and quantitative formation of the δ-lactone. The lactone showed: m.p. 136–137°; i.r. ν_{max} 1730 ($COOCH_3$), and 1725 cm^{-1} (δ-lactone); p.m.r. δ, 0.675 (s, 3H, C-14 CH_3), 1.16 (s, 3H, C-16 CH_3), 3.72 (s, 3H, $COOCH_3$), 3.66 and 4.20 (m, 2H, AB part of an ABX, J_{AB} = 11 Hz, J_{AX} = 5 Hz, and J_{BX} = 11 Hz; C-13 CH_2); mol. wt. 294 (mass spectrum).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36, H, 8.90. Found: C, 69.38; H, 8.83.

The similarity in coupling constants for the ABX system formed by the C-13 protons (H_A and H_B) and the C-8 proton (H_x) for the δ-lactone and hydroxy-acid **3** suggests, not unexpectedly, that the hydroxyl group of **3** hydrogen bonds with the carboxyl and that **3** adopts a conformation very similar to that of the δ-lactone.

Reduction of Methyl Esters

The same procedure was followed for the three esters, methyl 3-phenylpropionate, methyl cyclohexylcarboxylate, and methyl abietate **4**.

To a solution of 5.0 mmoles of an ester in 50 ml of dimethoxyethane were added 20 mmoles of sodium trimethoxyborohydride and the mixture stirred under reflux under a nitrogen atmosphere. Five millilitre aliquots of the reaction mixture were withdrawn at appropriate times, quenched in dilute acid and examined by p.m.r. spectroscopy for the extent of reduction. In all three cases it was possible to observe the rate of disappearance of the ester group by integrating the area under the ester methyl absorption and comparing it with the area under absorptions arising from protons common to both the starting ester and the alcohol products. The results are shown in Table I. The 3,5-dinitrobenzoate derivatives of the products were prepared in the usual way and gave satisfactory melting points. The p.m.r. spectra of the products were consistent with expected alcohols.

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1. H. C. BROWN and E. J. MEAD. J. Am. Chem. Soc. **75**, 6263 (1953).
2. E. Schenker. Angew. Chem. **73**, 81 (1961), and references therein.
3. R. H. BIBLE and R. R. BURTNER. J. Org. Chem. **26**, 1174 (1961).
4. L. A. PAQUETTE and N. A. NELSON. J. Org. Chem. **27**, 2272 (1962).
5. C. K. INGOLD and F. R. SHAW. J. Chem. Soc. 2918 (1927).
6. M. S. BROWN and H. RAPOPORT. J. Org. Chem. **28**, 3261 (1963).
7. R. PAUL and N. JOSEPH. Bull. Soc. Chim. France. 758 (1953); R. F. NYSTROM, S. W. CHAIKIN, and W. G. BROWN. J. Am. Chem. Soc. **71**, 3245 (1949); H. C. BROWN, E. J. MEAD, and B. C. SUBBA RAO. J. Am. Chem. Soc. 77, 6209 (1955).
8. H. C. BROWN and R. F. MCFARLIN. J. Am. Chem. Soc. **80**, 5372 (1958).
9. H. C. BROWN and C. J. SHOAF. J. Am. Chem. Soc. **86**, 1079 (1964); H. C. BROWN and P. M. WEISSMAN. J. Am. Chem. Soc. **87**, 5614 (1965).
10. G. HESSE and R. SCHRÖDEL. Ann. **607**, 24 (1957).

Chemistry of the aminochromes. Part XIII. Some further observations on the reactions of the aminochromes with thioglycollic acid[1,2]

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Thioglycollic acid reacts with adrenochrome in aqueous solution to give 5,6-dihydroxy-1-methylindole and 4-*S*-carboxymethylthio-5,6-dihydroxy-1-methylindole, together with smaller amounts of the lactone obtained by intramolecular cyclization of the latter compound. When the reaction is carried out in the absence of water the relative amount of 5,6-dihydroxy-1-methylindole formed is markedly reduced. At lower temperatures 4-*S*-carboxymethylthio-5,6-dihydroxy-1-methylindole is the main product obtained, whilst at higher temperatures the corresponding lactone predominates.

The major products obtained by the action of thioglycollic acid on 4- and 7-methyladrenochrome in aqueous solution were 5,6-dihydroxy-1,4-dimethylindole and 4-*S*-carboxymethylthio-5,6-dihydroxy-1,7-dimethylindole respectively.

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The reduction of adrenochrome (**1**) by thioglycollic acid was first reported in 1945 (1). Some years later an examination by paper chromatography of the products formed when this reaction was carried out in aqueous solution at room temperature, indicated that two major products were consistently obtained and that they were accompanied by lesser amounts of two other products (2). The two major products have subsequently been identified as 5,6-dihydroxy-1-methylindole (**2**) and 4-*S*-carboxymethylthio-5,6-dihydroxy-1-methylindole (**3**) (3). Analogous products also appear to be formed by the action of thioglycollic acid on related simple aminochromes (3).

In the past the preliminary examination of

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