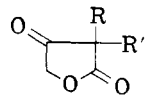
TABLE I

3,3-DISUBSTITUTED TETRONIC ACIDS



R	R′	B.p. °C./Mm.	n_D^{25}	Yield, %	Empirical Formula	Analyses, C and H Calcd.		Found	
CH_3	CH_3	42–44/0.5	1.4468	85	$C_6H_8O_3$[1]	56.24	6.29	55.98	6.36
C_2H_5	C_2H_5	219/760	1.4463	79	$C_8H_{12}O_3$[1a]	61.52	7.75	61.27	7.89
CH_3	n-C_4H_9	240–244/760	1.4475	75	$C_9H_{14}O_3$	63.51	8.29	63.28	8.34
C_2H_5	sec-C_5H_{11}	255/760	1.4655	68	$C_{11}H_{18}O_3$	66.64	9.15	66.55	9.19
CH_3	C_6H_5	292/760	1.5341	67	$C_{11}H_{10}O_3$	69.46	5.30	69.51	5.42

EXPERIMENTAL

Ethyl α,α-disubstituted acetoacetates. These esters were prepared according to a method recently described from this laboratory.[2] *Ethyl α,α-dimethylacetoacetate*[3] was obtained in 65% yield; b.p. 180–184°; n_D^{25} 1.4162. *Ethyl α,α-diethylacetoacetate*[4] was prepared in 79% yield; b.p. 99–103° (14 mm.); n_D^{25} 1.4300. *Ethyl α-methyl-α-n-butylacetoacetate* was prepared with a yield of 82%; b.p. 119–120° (16 mm.); n_D^{25} 1.4295.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.85; H, 9.88.

Ethyl α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in a yield of 66%; b.p. 107° (5 mm.); n_D^{25} 1.4418.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.54; H, 10.65.

Ethyl γ-bromo-α,α-disubstituted acetoacetic esters. The preparation of these compounds was according to the method of Conrad and Gast.[5] *Ethyl γ-bromo-α,α-dimethylacetoacetate*[5] was obtained in 73% yield; b.p. 117–119° (12 mm.); n_D^{25} 1.4651. *Ethyl γ-bromo-α,α-diethylacetoacetate*[1a] was prepared with a yield of 77%; b.p. 80° (1 mm.); n_D^{25} 1.4713. *Ethyl γ-bromo-α-methyl-α-n-butylacetoacetate* was obtained in 79% yield; b.p. 133° (4 mm.); n_D^{25} 1.4665.

Anal. Calcd. for $C_{11}H_{19}BrO_3$: C, 47.32; H, 6.85. Found: C, 46.95; H, 7.07.

Ethyl γ-bromo-α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in 55% yield; b.p. 131° (4 mm.); n_D^{25} 1.4671.

Anal. Calcd. for $C_{13}H_{23}BrO_3$: C, 50.82; H, 7.54. Found: C, 50.07; H, 7.64.

Ethyl γ-bromo-α-methyl-α-phenylacetoacetate was prepared in 51% yield; b.p. 165° (4 mm.); n_D^{25} 1.5306.

Anal. Calcd. for $C_{13}H_{15}BrO_3$: C, 52.18; H, 5.05. Found: C, 51.76; H, 5.43.

Ethyl γ-acetoxy-α,α-disubstituted acetoacetates. These esters were prepared by reaction of the above γ-bromo compounds with potassium acetate in alcohol.[5] *Ethyl γ-acetoxy-α,α-dimethylacetoacetate*[1b] was obtained in 80% yield; b.p. 89° (0.5 mm.); n_D^{25} 1.4319. *Ethyl γ-acetoxy-α,α-diethylacetoacetate*[1a] was obtained in 63% yield; b.p. 92° (0.25 mm.); n_D^{25} 1.4415. *Ethyl γ-acetoxy-α-methyl-α-n-butylacetoacetate* was prepared in 55% yield; b.p. 126° (1.5 mm.); n_D^{25} 1.4398.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.24; H, 8.85.

Ethyl γ-acetoxy-α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in 46% yield; b.p. 153° (5 mm.); n_D^{25} 1.4500.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.08; H, 8.95.

Ethyl γ-acetoxy-α-methyl-α-phenylacetoacetate was obtained in 47% yield; b.p. 171° (5 mm.); n_D^{25} 1.5002.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 65.03; H, 6.66.

3,3-Disubstituted tetronic acids. The preparation of 3-methyl-3-phenyltetronic acid will illustrate the method used for the synthesis of the compounds listed in Table I.

In a small distillation apparatus was placed 26 g. of ethyl γ-acetoxy-α-methyl-α-phenylacetoacetate. To this was added five drops of concentrated sulfuric acid and the flask was placed in an oil bath at 125°. The odor of ethyl acetate became noticeable after about 15 min. The mixture was held at 125° for 24 hr. During this time a small volume of distillate was collected and was identified as ethyl acetate. The remaining material was distilled under reduced pressure and that portion boiling at 145–150°/5 mm. was collected. A small sample on redistillation boiled at 292°/atm.

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Reduction of the Azido Group with Sodium Borohydride[1]

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Pyridinium salts, azomethine derivatives, and diazonium salts represent functional groups that have been reduced by sodium borohydride.[2] Nitro,[3] amide, imide, and nitrile groups are not generally attacked by this metal hydride[2] and its effect on other functional groups containing nitrogen has not been established. An extension of the selectivity of this reagent to organic azides is described here.

Both aliphatic and aromatic azides were reduced by lithium aluminum hydride (LAH) in good yields to the corresponding primary amines.[4] In

(1) Financial support by the Office of Ordnance Research, U. S. Army, under contracts No. DA-01-ORD-331 and DA-01-ORD-428.
(2) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York (1956), pp. 100, 750, 760, 773, 776, 781, 789, 806.
(3) C. E. Weill and G. S. Panson, *J. Org. Chem.*, **21**, 803 (1956) reported the reduction of nitrobenzene with sodium borohydride to azoxybenzene.
(4) J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 5865 (1951).

contrast, monofunctional aliphatic azides have now been recovered unchanged from prolonged exposure to sodium borohydride. Reduction of α-azidoketones proceeded smoothly with LAH to the corresponding α-amino-carbinol but a greater selectivity for the carbonyl group by sodium borohydride was found since azidocarbinols were obtained from azidoacetone and *p*-bromophenacyl azide. A smaller amount of an aminocarbinol was also obtained in the latter case. Attempts to reduce ethyl α-azido-α-phenylacetate with sodium borohydride led to an extremely poor yield of α-phenylglycine.

Aromatic azides underwent reduction by sodium borohydride with greater facility. The three isomeric azidobenzoic acids were reduced in good yield to the corresponding aminoacids and *p*-aminoanisole was obtained in moderate yield from *p*-azidoanisole. Curiously phenyl azide afforded only a trace of aniline, identified by its picrate derivative. A small amount of an unidentified liquid was also obtained and phenyl azide was recovered.

Resistance of amide and sulfonamide groups to reduction by sodium borohydride was demonstrated in the smooth transformation of benzoyl azide into benzamide (low yield) and methane-, benzene-, and *p*-toluenesulfonyl azides into the corresponding sulfonamides with this reagent.

Stoichiometry of the reduction of azido derivatives may be represented by the following statements; however, an excess of the reagent was used in each case to assure maximum reaction. The detection of an ammonia odor during certain reductions suggested that additional reaction sequences were also occurring.

$$4\ R{-}N_3 + NaBH_4 \longrightarrow (RNH)_4BNa + 4\ N_2$$

R = aryl, acyl or sulfonyl groups

$$4\ R{-}COCH_2N_3 + NaBH_4 \longrightarrow (R{-}\underset{\displaystyle CH_2N_3}{\underset{|}{CH}}{-}O{-})_4BNa$$

$$2\ R{-}CO{-}CH_2N_3 + NaBH_4 \longrightarrow (R{-}\underset{\displaystyle O^-}{\underset{|}{CH}}CH_2NH{-})_2BNa + 2\ N$$

R = alkyl or aryl groups

EXPERIMENTAL[5]

Three methods were used in the reduction of azides with sodium borohydride.

Method A. To a solution of 3.0 g. (0.080 mole) of sodium borohydride (98%, Metal Hydrides, Inc.) in 25 ml. of water and 10 ml. of purified dioxane was added a solution of 3.0 g. (0.020 mole) of *p*-azidoanisole in 25 ml. of dioxane. The solution was refluxed for 5 hr., cooled, and acidified with 10% hydrochloric acid. Ether extraction of the acidic solution yielded 0.8 g. of unreacted azide. Upon making the acidic water layer alkaline with 10% sodium carbonate there was obtained by ether extraction 2.1 g. of a mixture of unreacted azide and *p*-anisidine. After one recrystallization from hot water (Norite), 0.6 g. (24%) of *p*-anisidine, m.p. and mixture m.p. 61–62°,[6] was obtained.

Method B. To a solution of 6.1 g. (0.16 mole) of sodium borohydride in 30 ml. of water and 10 ml. of purified dioxane maintained at 30° with external cooling was added dropwise with stirring a solution of 2.0 g. (0.0083 mole) of *p*-bromophenacyl azide in 25 ml. of dioxane. The resulting solution was refluxed for 2 hr. (during which time an ammonia odor was detected), cooled, and acidified with 10% hydrochloric acid. The acidic solution was extracted with three 75-ml. portions of ether and the combined ethereal extracts washed with 50 ml. of distilled water and dried over anhydrous sodium sulfate. Ether was removed in an air stream and the residue dried *in vacuo*. Crude α-(azidomethyl)-*p*-bromobenzyl alcohol, 1.3 g. (65%), was purified by evaporative distillation at 0.03 mm. (bath temperature *ca.* 100°) until the m.p. was constant at 35.8–37.0° (corr.).

Anal. Calcd. for $C_8H_8BrN_3O$: C, 39.68; H, 3.33; Br, 33.01; N, 17.36. Found: C, 40.00; H, 3.59; Br, 33.11; N, 17.59.

The acidic water layer was boiled for ten minutes, cooled, made alkaline with 6*N* sodium hydroxide, concentrated until cloudy, filtered while hot, and allowed to cool. From the cold solution 0.2 g. (11%) of α-(aminomethyl)-*p*-bromobenzyl alcohol separated as colorless plates, m.p. 113°.[7] Ether extraction of the mother liquor yielded an additional 0.1 g. (total yield 17%) of the aminohydrin, m.p. 111.2–111.8° (corr.) after three recrystallizations from water.

Anal. Calcd. for $C_8H_{10}BrNO$: C, 44.46; H, 4.67; N, 6.48. Found: C, 44.73; H, 4.90; N, 6.44.

TABLE I

REDUCTIONS WITH SODIUM BOROHYDRIDE

Azide	Method	Corresponding Amine or Amide, %	M.P., °C.
n-Butyl-	A	0[a]	—
Cyclohexyl-	A	Trace[b]	—
Phenyl-	A	Trace[c]	—
Azidoacetone	B	0[d]	—
Benzoyl-	B	29[e]	129
Ethyl α-azido-α-phenylacetate	B	4[f]	250–259[f]
Methanesulfonyl-	B	39	91– 92[g]
Benzenesulfonyl-	B	65	153–155[h]
Tosyl-	B	39	137–138[i]
p-Azidobenzoic acid	C	87	190[j]
m-Azidobenzoic acid	C	69	176–177[k]

[a] *n*-Butyl azide recovered (78%). [b] Cyclohexylamine was isolated as its hydrochloride, m.p. 209–211°. [W. Markownikoff, *Ann.*, **302**, 1 (1898)]. [c] Aniline was isolated as its picrate derivative, m.p. 165–175° (dec.) [O. Silberrad and G. Rotter, *J. Chem. Soc.*, **89**, 167 (1906)]. A trace of an unidentified colorless liquid, b.p. 55° (4.3 mm.) was obtained and phenyl azide was recovered in low yield. [d] From azidoacetone and sodium borohydride (molar ratio 1:2.4), 1-azido-2-propanol, b.p. 31–34° (2.4 mm.), n_D^{25} 1.4525 [J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955)] was obtained in 28% yield after a reduction time of half an hour. An ammonia odor was detected during the reduction. [e] Continuous ether extraction of the acidified reaction mixture (reduction at room temperature) was followed by washing the crude product with 10% sodium bicarbonate. [f] Sublimation point. The product, α-phenylglycine, gave a positive Lassaigne test. [g] L. Field and P. H. Settlage, *J. Am. Chem. Soc.*, **77**, 170 (1955). [h] J. Stenhouse, *Ann.*, **140**, 284 (1866). [i] P. V. McKie, *J. Chem. Soc.*, **113**, 799 (1918). [j] J. Wilbrand and F. Beilstein, *Ann.*, **128**, 257 (1863). [k] E. Widnmann, *Ann.*, **193**, 202 (1878).

(5) Analyses by Midwest Micro-lab, Inc., Indianapolis.

(6) W. Lossen, *Ann.*, **175**, 313 (1875).

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The hydrochloride, m.p. 225.6–226.4° (dec.) (corr., bath preheated to 210°), was recrystallized from an ethanol and ether mixture.

Anal. Calcd. for $C_8H_{11}BrClNO$: C, 38.04; H, 4.39; N, 5.55. Found: C, 37.87; H, 4.51; N, 5.65.

Method C. In a solution of 20 ml. of water and 16 ml. of 5% sodium hydroxide was dissolved 3.3 g. (0.02 mole) of *o*-azidobenzoic acid. To this solution was added a solution of 3.0 g. (0.080 mole) of sodium borohydride in 25 ml. of water. After being refluxed for 5 hr. the solution was cooled and made acidic with 10% hydrochloric acid. Following treatment with 10% sodium hydroxide until basic, the solution was made acidic with glacial acetic acid and upon storage in the refrigerator overnight crude anthranilic acid, m.p. and mixture m.p. 148–149°,[8] 1.9 g. (69%), was obtained. Extraction of the mother liquor with ether yielded an additional amount of the product. Upon recrystallization from hot water, a second crop of crystals weighing 0.5 g. (total yield 85%), m.p. and mixture m.p. 146–147°, was obtained.

Additional examples for each procedure are found in Table I.

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Hydrogenolysis of Fatty Acid Esters of 4-Desoxypyridoxine[1]

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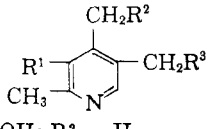
During the course of our investigation on the fatty acid esters of vitamin B_6, it was noted that the 5-ester linkage of 3,*O*-benzyl-4-desoxypyridoxine 5-palmitate (II) was cleaved when it was hydrogenated in the presence of platinum and palladium catalysts under 30 pounds pressure at room temperature. As was expected, debenzylation also took place during the treatment, and consequently free palmitic acid and 2,4,5-trimethyl-3-pyridinol (VII) were identified from the reaction mixture. Since this represented catalytic hydrogenolysis of the ester linkage, it appeared of interest to investigate further with some other derivatives of 4-desoxypyridoxine (I).



I, $R^1 = R^3 = OH$; $R^2 = H$
II, $R^1 = C_6H_5CH_2O—$; $R^2 = H$; $R^3 = CH_3(CH_2)_{14}COO—$
III, $R^1 = R^3 = CH_3COO—$; $R^2 = H$
IV, $R^1 = R^3 = CH_3(CH_2)_{14}COO—$; $R^2 = H$
V, $R^1 = CH_3(CH_2)_{14}COO—$; $R^2 = H$; $R^3 = OH$
VI, $R^1 = R^2 = OH$; $R^3 = H$
VII, $R^1 = OH$; $R^2 = R^3 = H$
VIII, $R^1 = CH_3(CH_2)_{14}COO—$; $R^2 = R^3 = H$

(1) This work was supported by research grant No. A-257 from the National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare.

When 4-desoxypyridoxine 3,5-dipalmitate(IV) or 4-desoxypyridoxine 3,5-diacetate(III) was similarly reduced, complete cleavage at the 5-position took place, and the 3-ester of 2,4,5-trimethyl-3-pyridinol(VII) was identified as a resultant compound. On the other hand, using 4-desoxypyridoxine(I) and 4-desoxypyridoxine 3-monopalmitate(V), it was found that when the 5-hydroxymethyl group was free, the reduction product was a mixture of compounds having a 5-hydroxymethyl group and a 5-methyl group. This indicates that cleavage of the 5-esters of 4-desoxypyridoxine(I) under 30 pounds hydrogen pressure in the presence of platinum and palladium catalysts at room temperature is direct hydrogenolysis and it is not catalytic hydrolysis of the ester linkage followed by reduction. Similar observation has been made with codecarboxylase, or vitamin B_6 5-phosphate.[2]

The ester linkage at the 3-position was hardly cleaved by hydrogenolysis. An attempt to isolate free palmitic acid from the hydrogenation mixture of 2,4,5-trimethyl-3-pyridinol palmitate(VIII) was unsuccessful, and the unchanged original compound was recovered.

It is known that pyridoxine can be directly reduced to 4-desoxypyridoxine(I)[3] or to a mixture of 4- and 5-desoxypyridoxines (I,VI).[2] Under the conditions presently employed, reduction of pyridoxine resulted in the formation of, among other compounds, 2,4,5-trimethyl-3-pyridinol(4,5-bisdesoxypyridoxine)(VII). 4-Desoxypyridoxine(I) as well as 5-desoxypyridoxine(VI) is a potential antivitamin B_6.[4] In the present study, 2,4,5-trimethyl-3-pyridinol(VII) was also found to be a reversible antagonist of pyridoxine to *Saccharomyces carlsbergensis*(ATCC 4228), and its inhibition potency was $^1/_8$ that of 4-desoxypyridoxine(I) on a molar basis.[5] The preparations of 2,4,5-trimethyl-3-pyridinol(VII) used for the test were obtained from 4-desoxypyridoxine(I) and from pyridoxine *via* bromination of the hydroxymethyl groups[6,7] followed by reduction.[3] The two preparations thus obtained showed an identical inhibition pattern for the growth of the assay organism eliminating the possibility that the inhibition might have been due

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(4) J. C. Rabinowitz and E. E. Snell, *Arch. Biochem. and Biophys.*, **43**, 399, 408 (1952).

(5) Assay conditions, see: L. Atkin, A. S. Schultz, W. L. Williams, and C. N. Frey, *Ind. Eng. Chem., Anal. Ed.*, **15**, 141 (1943).

(6) T. Sakuragi and F. A. Kummerow, *J. Am. Chem. Soc.*, **78**, 839 (1956).

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