117. *Observations on Steroidal 20-Keto-21-aldehydes.*

By E. Caspi and H. Zajac.

It has been shown that steroids with a dihydroxyacetone side-chain in the presence of catalytic amounts of acid undergo Mattox rearrangement to yield 20,21-glyoxals. In addition, small amounts of C_{19} 17-ketones were obtained, probably as a result of a reverse aldol reaction. The glyoxal, on oxidation with periodic acid, yielded the 17α-hydroxy-17β-carboxylic acid and the C_{19} 17-ketone. Treatment of the glyoxal with base led to a 17β-carboxylic acid and a 17β-hydroxymethyl derivative.

When a solution of cortisone was refluxed in the presence of catalytic amounts of toluene-*p*-sulphonic acid,[1] starting material was recovered which was accompanied by a small amount of adrenosterone. Since it was considered unlikely that the 17-ketone resulted from oxidative cleavage of the dihydroxyacetone portion, the reaction was further explored, as is described herein.

When a solution of cortisone in dioxan and ethyl methyl ketone was refluxed in the presence of catalytic amounts of toluene-*p*-sulphonic acid,[1] the recovered steroids consisted mainly of unchanged starting material from which a small amount of adrenosterone was isolated. When the reaction was carried out in the same manner but a portion of the solvent was slowly distilled off, two products were formed. The minor product was adrenosterone. The major product was a compound (Ia) $\lambda_{max.}$ 240 and 285 mμ, and on acetylation with pyridine–acetic anhydride gave the monoacetate (Ib), $\lambda_{max.}$ 243 mμ.[2] A nuclear magnetic resonance (n.m.r.) spectrum of the enol (Ia) had bands at τ 0·42 for the 21-aldehyde proton,[3] τ 4·26 for the 4-hydrogen atom, and τ 4·37 for the hydrogen atom on the enolic oxygen.

Analogous results were obtained for 17α,21-dihydroxypregn-4-ene-3,20-dione (Reich-

[1] Nussbaumer, Yuan, Robinson, Mitchell, Oliveto, Beaton, and Barton, *J. Org. Chem.*, 1962, **27**, 20.
[2] Dorfman, *Chem. Rev.*, 1953, **53**, 47.
[3] Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Ltd., London, 1959, p. 62.

stein's substance S) which yielded androst-4-ene-3,17-dione and the glyoxal (Ic), on acetylation of which the monoacetate (Id) was obtained. Confirmation of structures (Ia and c) was provided by syntheses.[4]

Undoubtedly, the aldehydes are formed by a Mattox rearrangement [5] of the dihydroxyacetone groupings. The formation of the 17-ketones could be rationalized as proceeding by a reverse aldol reaction, as indicated in (IIB). Interconversion of α-ketols (II) of the type (A and B) is well documented.[6,7]

When aldehyde (Ia) was treated with methanol and catalytic amounts of sulphuric acid, the expected 21,21-dimethoxypregn-4-ene-3,11,20-trione (III) was obtained. The n.m.r. spectrum of this triketone had bands at τ 5·64 for the 21-proton and a band equivalent to 6 protons at τ 6·59 for the two methoxy-groups. In (III), the chemical shift for the 21-hydrogen atom is at higher field (5·64) than in dioxolan (5·0—5·2) or naphthodioxan (5·3—5·5).[8,9]

Attempts were then made to cleave the enol aldehyde (Ia) oxidatively. However, the reaction did not proceed as expected. On treatment of a methanolic solution with aqueous periodic acid a neutral and an acidic product were obtained. The neutral compound proved to be adrenosterone, and the acid was identified as 17α-hydroxy-3,11-dioxoandrost-4-ene-17β-carboxylic acid (IVa). When the aldehyde (Ic) was oxidized, androst-4-ene-3,17-dione and 17α-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (IVb) were the products. Graber *et al.*[10] have observed the formation of α-glycols by the attack of periodic acid on a double bond. They have rationalized the reaction by assuming initial formation of an epoxide which is then opened to the glycol.[10] It appears that a similar reaction occurred in the present case and that the initial attack was on the 17,20-double bond.

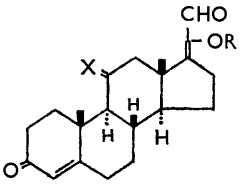
Compounds with α-dicarbonyl functions undergo benzilic acid rearrangements on treatment with base.[11] When a methanolic solution of the aldehyde (Ia) was treated with sodium methoxide, an acid and a neutral product were obtained. However, the acid proved to be 3,11-dioxoandrost-4-ene-17β-carboxylic acid (Va) and not the expected C_{21}-α-hydroxy acid. The neutral product (VIa) absorbed ultraviolet light at 239 mμ (ε 12,000) and its infrared spectrum showed bands at 3450, 1700, 1650, and 1610 $cm.^{-1}$; it was identified as its monoacetate (VIb) whose infrared spectrum was devoid of hydroxyl absorption. The formation of the C_{20} acid (Va) and of a monoalcohol ($C_{20}H_{28}O_3$) (VIa) suggested that cleavage of the 20,21-bond and disproportionation of the resulting product occurred. This suspicion was borne out since the alcohol was identified by an alternative synthesis through the acetate (VIb).

For this synthesis the 11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (Vc) was reduced with lithium aluminium hydride to a mixture of triols isomeric at position 3, from which the 3β-isomer (VII) was isolated. The 3β-hydroxy-configuration was assigned to this compound by analogy with previous observations [12] and on the basis of molecular rotational differences, [VIc] − [VII] = +174°. The allylic alcohols were oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone [13] to 11β-hydroxy-17β-hydroxymethylandrost-4-en-3-one (VIc). Acetylation of the diol (VIc) gave the 20-acetate (VId), which was oxidized

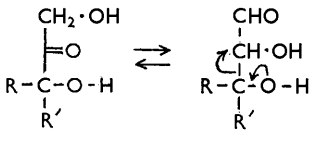
[4] Herzog, Gentles, Marshall, and Hershberg, *J. Amer. Chem. Soc.*, 1961, **83**, 4073.
[5] Mattox, *J. Amer. Chem. Soc.*, 1952, **74**, 4340.
[6] Wohl and Neuberg, *Ber.*, 1900, **33**, 3099; Bruyn, *Ber.*, 1895, **28**, 3078; Fischer, Taube, and Baer, *Ber.*, 1927, **60**, 479; Wolfrom and Lewis, *J. Amer. Chem. Soc.*, 1928, **50**, 837.
[7] von Euw and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 1140; Schindler, Frey, and Reichstein, *ibid.*, 1941, **24**, 360.
[8] Caspi, Wittstruck, and Piatak, *J. Org. Chem.*, 1962, **27**, 3183.
[9] Caspi, Wittstruck, and Grover, *J. Org. Chem.*, 1963, **28**, 763.
[10] Graber, Snoddy, Arnold, and Wendler, *J. Org. Chem.*, 1956, **21**, 1517; Chatterjee and Majumdar, *Analyt. Chem.*, 1956, **28**, 878.
[11] Wendler and Graber, *Chem. and Ind.*, 1956, 549; Hirschmann, Bailey, and Chemerda, *ibid.*, 1958, 682; Lewbart and Mattox, *J. Org. Chem.*, 1963, **28**, 1773, 1779, 2001.
[12] Caspi, Grover, Grover, Lynde, and Nussbaumer, *J.*, 1962, 1710.
[13] Burn, Petrow, and Weston, *Tetrahedron Letters*, 1960, No. 9, 14.

with chromium trioxide in pyridine to 17β-acetoxymethylandrost-4-ene-3,11-dione identical with the acetate (VIb) obtained previously.

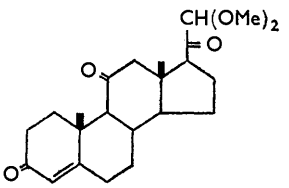
It seems possible that a nucleophilic attack of methoxide ions on C-21 (VIII) and the cleavage of the 20,21-bond with the indicated electron shift, followed by reprotonation at



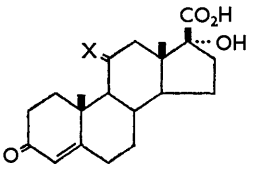
(I) a: R = H, X = O
b: R = Ac, X = O
c: R = H, X = H_2
d: R = Ac, X = H_2



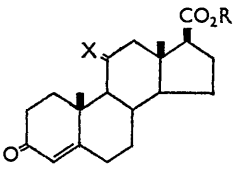
(A) (II) (B)



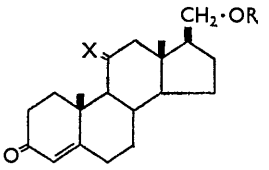
(III)



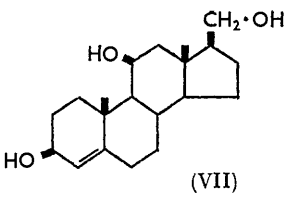
(IV) a: X = O
b: X = H_2



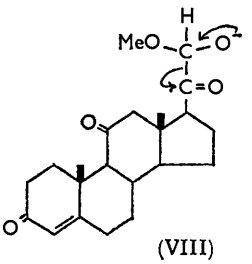
(V) a: R = H, X = O
b: R = Me, X = O
c: R = H, X = H, β-OH



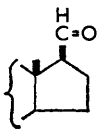
(VI) a: R = H, X = O
b: R = Ac, X = O
c: R = H, X = H, β-OH
d: R = Ac, X = H, β-OH



(VII)



(VIII)



(IX)

C-20, gave the aldehyde (IX); this could then disproportionate by the Cannizzaro reaction to yield the products (V) and (VI) observed. Apparently the course of reaction with methanolic sodium methoxide is different from that with methanolic sodium hydroxide. With sodium hydroxide, the glyoxals gave products of benzilic acid rearrangement with little, if any, C-20-21 cleavage.[11]

Experimental

Infrared spectra taken are for samples in potassium bromide in paper blotters. Ultraviolet spectra were taken for methanol solutions on a Cary spectrophotometer model 14. M. p.s were taken on a hot stage and are corrected. Nuclear magnetic resonance spectra were determined for deuterated chloroform or deuterated methanol solutions with tetramethylsilane as internal standard on a Varian spectrometer model 4300B.

20-*Hydroxy*-3,11-*dioxopregn*-4,17(20)-*dien*-21-*al* (Ia).—(*a*) A mixture of cortisone (660 mg.), ethyl methyl ketone (17 ml.), dry dioxan (17 ml.), and toluene-*p*-sulphonic acid (80 mg.) was slowly distilled for 5 hr. until 15 ml. of distillate were collected. Then pyridine (0·5 ml.) was added, followed by water, and the products were recovered with methylene chloride–ether (1 : 3). The extract was washed, dried, and concentrated to a residue (620 mg.). The syrupy residue was crystallized from ethyl acetate to yield the aldehyde (Ia) (172 mg.).

Chromatography of the crude mother-liquor gave additional amounts of this product (Ia) and adrenosterone. The adrenosterone had m. p. and mixed m. p. 220—223°, and its infrared spectrum was identical with that of an authentic sample.

When the reaction was carried out as above, but the solvent was not distilled, thin-layer chromatography of the recovered steroids [silica gel–ethyl acetate–chloroform (1 : 1)] led to isolation of cortisone and adrenosterone.

(*b*) A solution of cortisone (2 g.) in glacial acetic acid (250 ml.) was refluxed for 6 hr.[4] Most of the acid was removed in a stream of nitrogen, then water was added and the steroids were recovered with methylene chloride–ether (1 : 3). The extract was washed and dried, and on concentration the aldehyde (Ia) (422 mg.) was obtained. The second crop (280 mg.) was cortisone acetate, and the third crop (170 mg.) adrenosterone. The *aldehyde* had m. p. 195—200° alone or in mixture with the above sample, and the infrared spectra were indistinguishable.

A sample, crystallized from ethyl acetate, had m. p. 197—203°, $[\alpha]_D^{20}$ +182·4° (in chloroform), $\lambda_{max.}$ (in MeOH) 240 (ε 16,000) and 285 mμ (ε 12,500), $\nu_{max.}$ 3425, 3325, 1725, 1690, 1655, 1635, and 1600 cm.$^{-1}$, τ (in $CDCl_3$) 0·42 (21-H), 4·26, 4·37 (20-OH), 8·56 (19-Me), and 9·00 (18-Me) (Found: C, 73·6; H, 7·55. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7%).

The aldehyde (25 mg.) in pyridine (0·5 ml.) was treated with acetic anhydride (0·25 ml.) and kept for 16 hr. at room temperature. The resulting *acetate* (Ib) crystallized from ethyl acetate and had m. p. 210—212°, $\lambda_{max.}$ (in MeOH) 243 mμ (ε 23,000), $\nu_{max.}$ 1760, 1700, 1675, 1660, 1610, and 1200 cm.$^{-1}$, τ (in $CDCl_3$) 0·43, 4·28, 7·73 (OAc), 8·56 (19-Me), and 9·03 (18-Me) (Found: C, 71·9; H, 7·35. $C_{23}H_{28}O_5$ requires C, 71·85; H, 7·3%).

20-*Hydroxy*-3-*oxopregn*-4,17(20)-*dien*-21-*al* (Ic).—(a) A solution of 17α,21-dihydroxypregn-4-ene-3,20-dione (1 g.) in dioxan (27 ml.), containing ethyl methyl ketone (20 ml.) and toluene-*p*-sulphonic acid (100 mg.) was slowly distilled for 5 hr. until 20 ml. of distillate had been collected. The reaction mixture was cooled, pyridine (0·7 ml.) was added, and the steroids were recovered as described for (Ia). The obtained residue was crystallized from ethyl acetate, to yield the aldehyde (Ic) (314 mg. in two crops). Chromatography of the mother-liquor gave additional amounts of this and also androst-4-ene-3,17-dione.

(b) A solution of 17α,21-dihydroxypregn-4-ene-3,20-dione (Reichstein's substance S) (1 g.) in glacial acetic acid (100 ml.) was refluxed for 6 hr. Most of the solvent was removed in a stream of nitrogen, and after dilution with water the products were recovered with methylene chloride. The methylene chloride solution was washed, dried, and concentrated to a residue. The residue crystallized from ethyl acetate, to yield the aldehyde (Ic) (460 mg.), m. p. 176—180° in the first two crops. The third crop (26 mg.) was Reichstein's substance S 21-acetate.

The *aldehyde* (Ic) obtained in experiments (*a*) and (*b*) gave identical infrared spectra and did not depress mutually their m. p.s. A sample was crystallized from ethyl acetate to m. p. 175—180°, $[\alpha]_D^{20}$ +155·6° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 242 (ε 17,500) and 285 mμ (ε 11,500), $\nu_{max.}$ 3440, 1660, 1650, and 1610 cm.$^{-1}$, τ (in $CDCl_3$) 0·48, 4·22, 4·38, (20-OH) 8·79, and 9·00, τ (in CD_3·OD) 4·28, 8·75, and 9·06 (Found: C, 76·2; H, 8·9. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

The *acetate* (Ia) was prepared as described for (Ib) and was crystallized from ethyl acetate to m. p. 165—168°, $\lambda_{max.}$ (in MeOH) 244 mμ (ε 21,500), $\nu_{max.}$ 1755, 1650, 1645, and 1175 cm.$^{-1}$ (Found: C, 74·25; H, 8·0. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·2%).

17α-*Hydroxy*-3,11-*dioxoandrost*-4-*ene*-17β-*carboxylic Acid* (IVa).—To a solution of the aldehyde (Ia) (35 mg.) in methanol (4 ml.), a solution of periodic acid (60 mg.) in water (0·5 ml.) was added and the mixture was left at room temperature for 20 hr. After dilution with water, the steroids were recovered with methylene chloride–ether (1 : 3) and then partitioned with aqueous sodium hydrogen carbonate into neutral and acidic fractions. The acid (IVa), crystallized from ethyl acetate (6 mg.), had m. p. 270—275°. A sample prepared by the method of Simpson *et al.*,[14] had m. p. 272—275° (reported,[14] 273—277°) alone or in a mixture with the above sample. The infrared spectra of the two samples were identical.

From the neutral fraction, on crystallization, adrenosterone was obtained.

17α-*Hydroxy*-3-*oxoandrost*-4-*ene*-17β-*carboxylic Acid* (IVb).—(*a*) To the aldehyde (Ic) (45 mg.) in methanol (5 ml.) a solution of periodic acid (100 mg.) in water (1 ml.) was added, and the mixture was stored for 24 hr. at room temperature. The mixture was then processed as described for (IVa), to yield the acid (IVb) (20 mg.), m. p. 225—229°, and androst-4-ene-3,17-dione. An authentic sample of this acid, m. p. 226—229°, was prepared [14] from Reichstein's substance S, had the same infrared spectrum, and did not depress its m. p.

[14] Simpson, Tait, Wettstein, Neher, von Euw, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 1200.

21,21-*Dimethoxypregn*-4-*ene*-3,11-20-*trione* (III).—A mixture of the aldehyde (Ia) (50 mg.), methanol (2·5 ml.), and concentrated sulphuric acid (1 drop) was left at room temperature for 24 hr. After dilution with aqueous sodium hydrogen carbonate, the steroids were extracted with methylene chloride–ether (1 : 3). The extract was washed, dried, and concentrated to yield a syrup (55 mg.) which crystallized on trituration with ethyl acetate. Recrystallization from ethyl acetate gave the trione (III) m. p. 156—158° (reported,[15] 160—163°), $\lambda_{max.}$ (in MeOH) 239 mμ (ε 16,000), $\nu_{max.}$ 1710, 1700, 1670, 1615, and 1070 cm.$^{-1}$, τ (in $CDCl_3$) 4·27, 5·64 (21-H), 6·59 [21-$(OMe)_2$], 8·58 (19-Me), and 9·33 (18-Me) (Found: C, 71·0; H, 8·0. Calc. for $C_{23}H_{32}O_5$: C, 71·1; 8·3%).

3,11-*Dioxoandrost*-4-*ene*-17β-*carboxylic Acid* (Va).—(*a*) To a solution of the aldehyde (Ia) (50 mg.) in anhydrous methanol (2·5 ml.) a solution of sodium methoxide (5 mg.) in anhydrous methanol (0·5 ml.) was added, and the mixture was left for 24 hr. at room temperature. A yellow solid (8·6 mg.) was precipitated and separated. The filtrate was diluted with water and extracted with methylene chloride–ether (1 : 3), and the extract was washed, dried, and concentrated to yield a neutral residue (22 mg.). From the aqueous phase, after acidification with 2N-hydrochloric acid, the acid (Va) was recovered with methylene chloride–ether (1 : 3). The extract was washed, dried, and concentrated to yield the product (Va) (8 mg.), m. p. 265—270° (reported,[16] 266—272°).

The ester (Vb), prepared by treatment of the acid with an excess of ethereal diazomethane, had m. p. 174—176° (reported,[16] 174—178°).

(*b*) The acid 11β-hydroxy-3-oxoandrost-4-ene-17β-carboxylic acid (Vc) was prepared from corticosterone.[16,17] A solution of it (50 mg.) in pyridine (0·3 ml.) was added to a suspension of chromium trioxide (100 mg.) in pyridine (0·5 ml.), and the mixture was left for 3 hr. at room temperature. Ethyl acetate was added and the steroid was recovered as previously described, to yield the acid (Va), m. p. 263—270°. The acid, with ethereal diazomethane, yielded the ester (Vb), m. p. 174—176°.

The acids and esters prepared in experiments (*a*) and (*b*) gave identical infrared spectra and did not depress mutually their m. p.s.

17β-*Acetoxymethylandrost*-4-*ene*-3,11-*dione* (VIb).—(*a*) To a solution of the hydroxy-diketone (VIa) (5 mg.) in pyridine (0·1 ml.), acetic anhydride (0·1 ml.) was added and the mixture was stored for 16 hr. at room temperature. This gave the acetate (VIb), m. p. 150—155°.

(*b*) A solution of compound (VId) (50 mg.) in pyridine (0·5 ml.) was treated with a suspension of chromic acid (35 mg.) in pyridine (0·5 ml.). After 3 hr. at room temperature the reaction mixture was worked up in the conventional manner to yield the *acetate* (VIb). It was crystallized twice from methanol–ether to m. p. 153—155° alone and in a mixture with the above sample, $[\alpha]_D$ +152·2° (in $CHCl_3$), $\lambda_{max.}$ (in MeOH) 239 mμ (ε 16,000), $\nu_{max.}$ 1740, 1700, 1670, 1620, and 1250 cm.$^{-1}$ (Found: C, 73·8; H, 8·1. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

17β-*Hydroxymethylandrost*-4-*ene*-3β,11β-*diol* (VII).—The acid (Vc) was prepared by treatment of a methanolic solution of corticosterone with aqueous periodic acid. To a solution of the acid (1·48 g.) in dry ether–tetrahydrofuran (1 : 1) (600 ml.), lithium aluminium hydride (5 g.) was added and the mixture was refluxed with exclusion of moisture for 4 hr. The reaction was terminated with acetone, then water was added and the precipitated solid was filtered off through Celite. The filtrate was concentrated to a small bulk, then diluted with water, and the steroids were extracted with methylene chloride–ether (1 : 3). The extract was washed, dried, and concentrated to yield a mixture of the epimeric triols (1·12 g.). This was crystallized twice from acetone to yield the *product* (VII), m. p. 143—145°, $[\alpha]_D^{19}$ +68·7° (in MeOH), $\lambda_{max.}$ (in MeOH) no specific absorption in the 220—240 mμ region, $\nu_{max.}$ 3350 (broad), 1035, and 995 cm.$^{-1}$ (Found: C, 74·9; H, 10·1. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%).

11β-*Hydroxy*-17β-*hydroxymethylandrost*-4-*en*-3-*one* (VIc).—To a solution of the triol (VII) (500 mg.) in anhydrous dioxan (6 ml.), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (600 mg.) was added and the mixture was agitated for 2 hr. with exclusion of moisture. The precipitate

[15] Simpson, Tait, Wettstein, Neher, von Euw, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 1163.

[16] Reichstein, *Helv. Chim. Acta*, 1937, **20**, 953; Mason, Myers, and Kendall, *J. Biol. Chem.*, 1936, **114**, 613.

[17] von Euw and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 988.

was filtered off and the filtrate was concentrated to a small bulk. The residue was dissolved in methylene chloride–ether (1 : 3), then washed 3 times with 2N-sodium hydroxide, then with water, twice with 2N-hydrochloric acid, and again with water, dried, and concentrated, to yield the crystalline **3-*ketone*** (VIc) (400 mg.). A sample, crystallized several times from methanol, had m. p. 205—207°, $[\alpha]_D^{19}$ +124° (in MeOH), $\lambda_{max.}$ (in MeOH) 242 mμ (ε 15,500), $\nu_{max.}$ 3500, 3380, 1650, and 1600 cm.$^{-1}$ (Found: C, 75·4; H, 9·50. $C_{20}H_{30}O_3$ requires C, 75·45; H, 9·4%).

17β-*Acetoxy*-11β-*hydroxymethylandrost*-4-*en*-3-*one* (VId).—A mixture of the alcohol (VIc) (400 mg.), pyridine (5 ml.), and acetic anhydride (2·5 ml.) was left for 16 hr. at room temperature. After the conventional working up, the *acetate* (VId) was obtained (340 mg.), that, crystallized from ethyl acetate, had m. p. 148—159°, $\nu_{max.}$ 3450, 1740, 1655, and 1615 cm.$^{-1}$ (Found: C, 72·6; 72·9; H, 8·85; 9·0. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

This work was supported by the U.S. Public Health Service. The receipt (by E. C.) of a U.S. Public Health Service Career programme award from National Cancer Institute and (by H. Z.) of a Post Doctoral Fellowship is acknowledged.

WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY,
SHREWSBURY, MASS., U.S.A.

[*Received, June 10th,* 1963.]