648. *Organic Fluorine Compounds. Part XVI.* The Preparation and Reactions of Ethyl Ethoxalylfluoroacetate.*

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The influence of reaction conditions on the yield of ethyl ethoxalylfluoroacetate has been studied. The sodio-derivative of this compound gives *C*-acyl derivatives on treatment with chlorides of carboxylic acids or benzenesulphonyl chloride; hydrolysis of these acyl derivatives has been investigated. The properties of ethyl bromoethoxalylfluoroacetate are described.

The synthesis[1] of ethyl ethoxalylfluoroacetate from diethyl oxalate and ethyl fluoroacetate in the presence of sodium ethoxide or sodium hydride gives yields of 40% (in benzene) to 50% (in ether). Increasing the amount of condensing agent decreases the yield, *e.g.*, with double the theoretical quantity of sodium ethoxide to 15—20%. An excess of diethyl oxalate has no beneficial influence; sodium hydride gives better yields than sodium methoxide, ethoxide, or t-butoxide.

These observations can be related to two facts: the condensation leads to an equilibrium, and ethyl sodioethoxalylfluoroacetate is split by the alcohol set free in the condensation:

$$[RO_2C{\cdot}CO{\cdot}CF{\cdot}CO_2R]^-Na^+ + 2R'OH \rightleftharpoons RO_2C{\cdot}CO_2R' + CH_2F{\cdot}CO_2R + NaOR' \rightleftharpoons$$
$$RO_2C{\cdot}CO_2R' + [CHF{\cdot}CO_2R]^-Na^+$$

This fission was realised for ethyl sodioethoxalylfluoroacetate, prepared from the pure ester, and the solid product obtained in the condensation always contained a significant amount of the sodio-derivative of ethyl fluoroacetate. Under the best conditions (see p. 3226) the yield in this condensation was 55%. As a by-product, ethyl α-ethoxalyl-αγ-difluoroacetoacetate was obtained in 12—15% yield; its structure followed from its analysis, non-reactivity with periodate, and partial hydrolysis to βδ-difluoro-αγ-dioxovaleric acid, isolated as its propyl ester, though in small yield. (The absence of a colour reaction with ferric chloride proved, in any event, that this compound was not the difluoro-derivative $EtO_2C{\cdot}CHF{\cdot}CO{\cdot}CO{\cdot}CHF{\cdot}CO_2Et$, the parent of which had been obtained[2] in the analogous reaction between diethyl oxalate and ethyl acetate.)

It was to be expected that the above complex equilibrium would be affected by the

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* Part XV, *Nature*, 1960, **185**, 529.

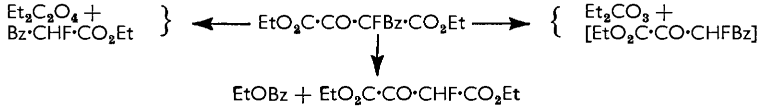
[1] Blank, Mager, and Bergmann, *Bull. Res. Council Israel*, 1957, **3**, 101.

[2] Fittig, Daimler, and Koller, *Ber.*, 1887, **20**, 202, 3183; *Annalen*, 1888, **249**, 182; Wislicenus, *Ber.*, 1887, **20**, 590; *Annalen*, 1888, **246**, 328; Hantzsch and Zeckendorf, *Ber.*, 1887, **20**, 1309.

solvent. Indeed the yield was 68% on condensation in tetrahydrofuran whose value for such reactions has been reported by Lawesson and Busch.[3]

In view of the above by-product the acylation of ethyl sodioethoxalylfluoroacetate was studied systematically. Benzoyl chloride, acetyl chloride, ethyl chloroformate, and benzenesulphonyl chloride gave acyl derivatives which might be *C*- or *O*-acyl derivatives. That benzenesulphonyl chloride reacted like other chlorides, made the latter improbable. Moreover, partial hydrolysis of the benzoyl derivative with hydrobromic acid in acetic acid (aqueous acid was ineffective) gave α-benzoyl-α-fluoropyruvic acid, isolated as its 2,4-dinitrophenylhydrazone.

The main products of this treatment were always fluoropyruvic acid and the acid corresponding to the acyl radical; only in the two cases mentioned above, were *C*-acyl derivatives of fluoropyruvic acid isolated. Alkoxides caused complete fragmentation of the acyl derivatives: *e.g.*, the benzoylation product and sodium ethoxide gave ethyl benzoate, diethyl oxalate, diethyl carbonate, ethyl α-benzoyl-α-fluoroacetate and ethyl ethoxalylfluoroacetate (the last two as their sodio-derivatives); the remaining fragment, ethyl benzoylfluoropyruvate, has not been isolated.



$$\begin{tikzcd} \left.\begin{matrix}Et_2C_2O_4 + \\ Bz\cdot CHF\cdot CO_2Et\end{matrix}\right\} & EtO_2C\cdot CO\cdot CFBz\cdot CO_2Et \arrow[l] \arrow[r] \arrow[d] & \left\{\begin{matrix}Et_2CO_3 + \\ [EtO_2C\cdot CO\cdot CHFBz]\end{matrix}\right. \\ & EtOBz + EtO_2C\cdot CO\cdot CHF\cdot CO_2Et & \end{tikzcd}$$

The product from ethyl sodioethoxalylfluoroacetate and ethyl chloroformate was broken down almost entirely in one direction, giving diethyl carbonate and ethyl ethoxalylfluoroacetate (as sodio-derivative); only very small amounts of diethyl fluoromalonate (and diethyl oxalate) were formed in addition.

It has been shown[4] that the sodio-derivative of ethyl ethoxalylfluoroacetate reacts with bromine, to give the bromo-derivative; this reaction fails if the free ester is treated with bromine or *N*-bromosuccinimide. The bromine in ethyl α-bromo-α-ethoxalyl-α-fluoroacetate is " positive: " sodium ethoxide regenerates ethyl ethoxalylfluoroacetate; diethyl sodiomalonate has the same effect, yielding diethyl bromomalonate. In the Experimental Part, better conditions for the preparation of the bromo-compound and of bromofluoropyruvic acid are described, based on these observations.

EXPERIMENTAL

Preparation of Ethyl Ethoxalylfluoroacetate.—To a stirred suspension (24 g., 1 mole) of sodium hydride in ether (750 ml.), diethyl oxalate (150 g., 1 mole), ethyl fluoroacetate (10 ml.), and a few drops of anhydrous ethanol were added, and the mixture was refluxed until the evolution of hydrogen set in and the product became yellow. The remainder (96 g., in all 1 mole) of ethyl fluoroacetate was then added at such a rate that the ether continued to boil gently. After 15 hr. at room temperature, the mixture was cooled to −15° and 50% hydrochloric acid (200 ml.) added slowly, so that the temperature did not exceed 0°. (If the temperature rises at this point, the yield is lower than expected.) The organic layer was separated and the aqueous phase extracted with benzene (100 ml.). The combined organic solutions were dried and concentrated at 60°/1 atm. and finally at 25 mm. (the fraction thus obtained contained ethyl fluoroacetate, which can be isolated by re-distillation in an efficient column). The residue was distilled at 1·5 mm.; under these conditions the excess of diethyl oxalate boiled at 55—57°, and the product at 95—98°. The distillation was repeated in a short column; the yield was 110—115 g. (55%). The residue boiled at 165—166°/0·1 mm. and was ethyl α-ethoxalyl-αγ-difluoroacetoacetate (see below). When the reaction was carried out in benzene under the same conditions, the yield was only 35%. It was raised again to 45% when, before the decomposition, 450 ml. of the solvent were distilled off at 50 mm. so that the ethanol formed in the reaction was removed.

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[3] Lawesson and Busch, *Acta Chem. Scand.*, 1959, **13**, 1717.

[4] Bergmann and Shahak, *J.*, 1960, 462.

The presence of the sodio-derivative of ethyl fluoroacetate in the crude product of the condensation was established by reaction with benzoyl chloride. From the product, obtained as above from sodium hydride (9·6 g.), diethyl oxalate (60·0 g.), and ethyl fluoroacetate (42·5 g.) in benzene (250 ml.), 150 ml. of the solvent were distilled off at 25 mm. and freshly distilled benzoyl chloride (56 g.) in benzene (100 ml.) was added. The whole was refluxed with stirring for 3 hr., then cooled and poured into water containing 50 ml. of concentrated hydrochloric acid. After removal of the benzene at 25 mm., distillation at 1 mm. gave ethyl α-benzoyl-α-fluoroacetate,[5] b. p. 125—127° (16 g., 19%), identified as its 2,4-dinitrophenylhydrazone, m. p. 190°, and ethyl α-benzoyl-α-fluoro-α-oxaloacetate, b. p. 162—165° (57 g., 46%).

Preparation of Ethyl Ethoxalylfluoroacetate in Tetrahydrofuran.—To a suspension of sodium hydride (24 g.) in tetrahydrofuran (300 ml.) and diethyl oxalate (150 g.), ethyl fluoroacetate (10 g.) was added and the mixture heated until a yellow colour appeared and the evolution of hydrogen set in. Then, the balance (96 g.) of ethyl fluoroacetate was added at such a rate that the solution refluxed gently. The mixture was refluxed, with stirring, for 2·5 hr., then cooled to −10° and poured into benzene (150 ml.), ice (150 g.), and concentrated hydrochloric acid (110 ml.). The aqueous phase was separated and extracted with benzene (50 ml.), and the combined organic phase dried and distilled *in vacuo*. Thus, ethyl ethoxalylfluoroacetate (139 g., 68%), b. p. 96—98° 1 mm., and ethyl α-ethoxalyl-αγ-difluoroacetoacetate (7 g.), b. p. 160—165°/0·05 mm., were obtained.

Reversal of the Condensation.—At 0°, ethyl ethoxalylfluoroacetate (41 g., 0·2 mole) was added to a suspension of sodium hydride (9·6 g., 0·4 mole) in ether (200 ml.) and the whole stirred at this temperature for 3 hr. Light petroleum (b. p. 40—60°) (200 ml.) was added and the solid product filtered off. Distillation of the filtrate in an efficient column gave ethyl fluoroacetate (3—5 g.), b. p. 116—117° (identified as the amide, m. p. 108°), diethyl oxalate (16 g.), b. p. 90—92°/25 mm., and ethyl oxalylfluoroacetate (8 g.), b. p. 140—142°/25 mm. Decomposition of the solid phase with concentrated hydrochloric acid (10 ml.) and ether (100 ml.), treatment of the ether extract with sodium hydrogen carbonate solution, and distillation gave ethyl fluoroacetate (8 g.). This proves that the reaction yielded ethyl fluoroacetate both in its free form and as sodio-derivative.

Ethyl α-Bromo-α-ethoxalyl-α-fluoroacetate.—From the product obtained as described above, half of the benzene (375 ml.) was distilled off in a column (50 mm., bath-temp. 40—45°), and the residue was cooled, diluted with dry benzene (300 ml.), and treated with bromine (stirring) at $\not>$35°. When the colour of the halogen remained [usually 140—150 g. (0·9 mole) of bromine], stirring was continued for 10 min. and the product poured into ice-water (500 ml.) which contained a little sulphur dioxide. The organic layer was washed with water, dried, and distilled, first at 30 mm., then at 1—1·5 mm. The product (170—175 g., 60—62%) boiled at 94—96°/0·5 mm. The yield is somewhat higher than that of ethoxalylfluoroacetate prepared under analogous conditions.

Bromofluoropyruvic Acid.—When the preceding compound (57 g.) had been treated with 20% hydrochloric acid (100 ml.) for 15 min. at room temperature and for 3 hr. under reflux, removal of the water under 30 mm. and distillation gave bromofluoropyruvic acid, b. p. 95—97°/0·5 mm. (24 g., 65%; lit.,[4] 35%). Trituration of the product with benzene and recrystallisation therefrom gave the acid, m. p. 102—103° (Found: C, 19·8; H, 1·4; F, 10·6; Br, 42·9. Calc. for $C_3H_2BrFO_3$: C, 19·5; H, 1·1; F, 10·3; Br, 43·2%). A small higher-boiling fraction (160°/1 mm.) was also secured; although it was not pure (Found: C, 23·8; H, 1·0; F, 8·5. Calc. for C_4BrFO_4: C, 22·7; H, 0; F, 9·0%), it appears to be the bromofluoro-oxaloacetic anhydride as successive treatment with water and diazomethane gave *methyl α-bromo-α-fluoro-α-methoxalylacetate*, b. p. 90—91°/0·5 mm. (Found: C, 28·2; H, 2·5; F, 7·7. $C_6H_6BrFO_5$ requires C, 28·0; H, 2·3; F, 7·4%). This has maxima at 1845 and 1750 cm.$^{-1}$ (C=O) and a shoulder at 1780 cm.$^{-1}$. According to Stork and Breslow,[6] five-membered cyclic anhydrides absorb at 1865 and 1782 cm.$^{-1}$; the ketonic-carbonyl of cyclopentanone causes a peak at 1745 cm.$^{-1}$. The C–F frequency was observed at 1015 cm.$^{-1}$.

Mesoxaldehydic acid bis-2,4-dinitrophenylhydrazone, obtained from bromofluoropyruvic acid and 2,4-dinitrophenylhydrazine as described before,[4] had m. p. 260° (decomp.) (Found: C, 38·6; H, 2·3; N, 24·0. Calc. for $C_{15}H_{10}N_8O_{10}$: C, 39·0; H, 2·2; N, 24·2%).

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[5] Bergmann, Cohen, and Shahak, *J.*, 1959, 3278.

[6] Stork and Breslow, *J. Amer. Chem. Soc.*, 1953, **75**, 3291.

Ethyl Bromofluoropyruvate.—This was obtained directly from ethyl bromoethoxalylfluoroacetate (28·5 g.) by hydrolysis with toluene-*p*-sulphonic acid sesquihydrate (5 g.) and water (1 ml.). The mixture was heated slowly until the temperature reached 150—160°. At this point, a reaction set in and ethanol distilled. The residue was heated at 180° for 10 min., then distilled at 1 mm. Redistillation through a short column gave the *ester* (10·5 g., 50%), b. p. 90—92°/30 mm. (Found: C, 28·4; H, 3·1; F, 8·6. $C_5H_6BrFO_3$ requires C, 28·2; H, 2·8; F, 8·9%).

Reaction of Ethyl Bromoethoxalylfluoroacetate with Sodium Ethoxide.—At $<10°$, ethyl bromoethoxalylfluoroacetate (28·5 g.) was added slowly to a suspension of sodium ethoxide (6·8 g.) in benzene (100 ml.). When the exothermic reaction had subsided, the product was poured into ice-cold 10% hydrochloric acid (50 ml.). The benzene layer gave, on distillation, ethyl ethoxalylfluoroacetate (11·5 g., 60%), b. p. 98°/0·8 mm., which was identified by its ferric chloride reaction and analysis.

Reaction of Ethyl Bromoethoxalylfluoroacetate with Diethyl Sodiomalonate.—A mixture of sodium hydride (2·4 g.), diethyl malonate (16·6 g.), and benzene (150 ml.) was stirred for 30 min. at room temperature, and ethyl bromoethoxalylfluoroacetate (28·5 g.) was added at such a rate that the temperature did not exceed 30°. After 12 hr. at room temperature, the product was poured into ice-cold 10% hydrochloric acid (50 ml.), and the benzene layer dried and distilled through a column, giving diethyl bromomalonate (15 g., 60%), b. p. 78—80°/0·5 mm. (Found: C, 35·6; H, 4·9. Calc. for $C_7H_{11}BrO_4$: C, 35·2; H, 4·6%), and ethyl ethoxalylfluoroacetate (14 g., 70%), b. p. 95°/0·6 mm. (Found: C, 46·3; H, 5·1; F, 8·8. Calc. for $C_8H_{11}FO_5$: C, 46·6; H, 5·3; F, 9·2%).

Diethyl Ethoxalylfluoromalonate.—Ethyl chloroformate (104 g.) was added to ethyl sodioethoxalylfluoroacetate which had been prepared from sodium hydride (24 g.), diethyl oxalate (146 g.), and ethyl fluoroacetate (106 g.) in benzene (750 ml.) and freed from alcohol by distillation *in vacuo* of part of the benzene (400 ml.) at 30—40°. The mixture was refluxed for 3 hr. with stirring. After cooling, the product was poured into water and the organic layer dried and distilled. After a fraction of diethyl oxalate (b. p. 50—55°/1 mm.), the *product* (171 g., 61%) boiled at 135—136°/1 mm. and had $\nu_{max.}$ (liquid) 1740 (broad; shoulder at 1785) and 1025 cm.$^{-1}$ (C—F) (Found: C, 47·7; H, 5·5; F, 7·0. $C_{11}H_{15}FO_7$ requires C, 47·5; H, 5·4; F, 6·8%).

Ethyl α-Benzoyl-α-ethoxalyl-α-fluoroacetate.—This *ester*, b. p. 162—165°/18 mm., was obtained analogously in 45% yield (139 g.) (Found: C, 57·8; H, 5·8; F, 6·4. $C_{15}H_{15}FO_6$ requires C, 58·1; H, 4·8; F, 6·1%). It was accompanied by diethyl oxalate and ethyl benzoylfluoroacetate, b. p. 125—127°/1 mm. (43 g., 20%), formed by sodium ethoxide-fission of the main product (see below); it gave a 2,4-dinitrophenylhydrazone, m. p. 190°.

Ethyl α-ethoxalyl-α-fluoroacetoacetate, b. p. 105—107°/1 mm., was prepared in 48% yield (119 g.) by using acetyl chloride (Found: C, 48·2; H, 5·3; F, 7·9. $C_{10}H_{13}FO_6$ requires C, 48·4; H, 5·2; F, 7·7%).

Ethyl α-benzenesulphonyl-α-ethoxalyl-α-fluoroacetate, b. p. 169—170°/0·5 mm. (yield, 57%), was synthetised analogously (Found: C, 48·8; H, 4·6; F, 5·1. $C_{14}H_{15}FO_7S$ requires C, 48·6; H, 4·3; F, 5·5%). The infrared spectrum showed, in the carbonyl region, an intense peak at 1750 and a smaller one at 1675 cm.$^{-1}$. The C–F frequency was at 1030 cm.$^{-1}$. For the sulphone group, intense bands at 1335—1310 and 1160—1130 cm.$^{-1}$, have been found to be characteristic.[7] In this region, intense bands were observed at 1130, 1200, 1310, 1390 cm.$^{-1}$.

Ethyl α-ethoxalyl-αγ-difluoroacetoacetate was isolated from the higher fractions formed in the condensation of diethyl oxalate and ethyl fluoroacetate; yields up to 15% were obtained when sodium ethoxide was used as condensing agent. The ester boiled at 175—177°/1·2 mm. and had $\nu_{max.}$ (liquid) 1740—1770 (C=O) and 1025 cm.$^{-1}$ (C–F) (Found: C, 45·2; H, 4·7; F, 14·5. $C_{10}H_{12}F_2O_6$ requires C, 45·1; H, 4·5; F, 14·3%).

Hydrolyses.—(*a*) The acylated product (0·05 mole) in anhydrous ethanol (50 ml.) was treated at ≯35° with alcoholic potassium hydroxide until the solution remained alkaline for some time (0·2—0·25 mole of hydroxide required). The solution was then heated and filtered and the solid extracted with 150 ml. of boiling anhydrous alcohol. The solid residue consisted of potassium oxalate and a little potassium fluoride. The combined alcoholic solutions were evaporated to dryness *in vacuo*, and this residue was filtered and washed with ether. From diethyl ethoxalylfluoromalonate, potassium fluoroacetate was thus obtained [identified, by successive treatment with thionyl chloride and ammonia, as fluoroacetamide, m. p. 106° (from

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[7] Barnard, Fabian, and Koch, *J.*, 1949, 2442; Schreiber, *Analyt. Chem.*, 1949, **21**, 1168.

chloroform)]; ethyl ethoxalylfluoroacetoacetate gave potassium acetate (identified as 4-phenylphenacyl ester, m. p. 110°); ethyl benzenesulphonylethoxalylfluoroacetate gave potassium benzenesulphonate (identified as benzylthiouronium salt, m. p. 150°). Ethyl ethoxalyldifluoroacetoacetate gave no alcohol-soluble salt.

(*b*) Acetic acid and 48% hydrobromic acid caused complete hydrolysis in 2 hours' refluxing. From the solution, fluoropyruvic acid was isolated (as 2,4-dinitrophenylhydrazone), and from the benzoyl derivative also benzoic acid. In the latter case, the dinitrophenylhydrazone was accompanied by a second, dark red one which was insoluble in all organic solvents, melted at 260—262° (decomp.), and exploded on attempted combustion analysis. It appeared to be *benzoylfluoropyruvic acid bis-2,4-dinitrophenylhydrazone* (Found: N, 19·4. $C_{22}H_{15}FN_8O_{10}$ requires N, 19·7%).

(*c*) Acetic acid was added to ethyl ethoxalyldifluoroacetoacetate (27 g.) and 48% hydrobromic acid (10 ml.) until a homogeneous solution resulted. After 1 hour's refluxing the solution was diluted with water (25 ml.), neutralised with sodium hydrogen carbonate, and extracted with ether (which dissolved only traces of organic matter). To the alkaline aqueous solution propyl alcohol (100 ml.), and then a mixture of propyl alcohol (50 ml.) and concentrated sulphuric acid (12 g.), were added. Sodium sulphate was filtered off and the clear solution azeotropically distilled with benzene (100 ml.). When no more water collected, the product was neutralised with solid sodium hydrogen carbonate, and the filtered solution was distilled, giving *propyl fluoropyruvate* (8·5 g.), b. p. 78—80°/1 mm. (Found: C, 49·3; H, 6·2; F, 12·5. $C_6H_9FO_3$ requires C, 48·7; H, 6·2; F, 13·0%), and *propyl βδ-difluoro-αγ-dioxovalerate* (2·5 g.), b. p. 102—103°/1 mm. (Found: C, 46·5; H, 5·2; F, 18·0. $C_8H_{10}F_2O_4$ requires C, 46·2; H, 5·0; F, 18·3%), which gave a strong red colour reaction with ferric chloride.

Alcoholyses.—(*a*) To diethyl ethoxalylfluoromalonate (28 g.) in methanol (60 ml.) a solution from sodium (2·3 g.) in methanol (100 ml.) was added at ≯20° with stirring. Benzene (50 ml.) and hydrochloric acid were added until the mixture was acidic, and the benzene solution was concentrated. The residue (15 g., 75%) was distilled *in vacuo* and identified as ethyl ethoxalylfluoroacetate.

After the ester (28 g.) had been added at 10° to a suspension of sodium methoxide (5·4 g.) in ether (100 ml.), addition of low-boiling light petroleum (50 ml.), filtration, and distillation gave ethyl methyl carbonate (6 g., b. p. 104—108°) and ethyl methyl oxalate (0·5 g.; b. p. 165—170°; identified as oxanilide, m. p. 242°). The solid product was treated with dilute hydrochloric acid and an excess of ether, and the residue from this ethereal extract was fractionated twice at 1 mm. The products consisted of diethyl fluoromalonate (0·3 g.), b. p. 82—83°/1 mm. (identified as the diamide,[8] m. p. 188—189°), and ethyl ethoxalylfluoroacetate (12·5 g., 62%), b. p. 98—99°/1 mm.

(*b*) Ethyl benzoylethoxalylfluoroacetate (62 g.) was added at ≯10° to a suspension of sodium ethoxide (13·6 g.) in anhydrous ether (150 ml.). After addition of low-boiling light petroleum (100 ml.), the solid product was filtered off and the solution fractionated through a column, giving diethyl carbonate, mainly boiling at 123—124° (2 g.), diethyl oxalate, b. p. 175—185° (11 g.) (identified by hydrolysis to the acid), and ethyl benzoate, b. p. 208—218° (15 g.; identified as acid). The solid product was treated with dilute hydrochloric acid and extracted with ether. Distillation of the residue from this extract at 1 mm. gave ethyl ethoxalylfluoroacetate, b. p. 95—102° (16 g.), and ethyl benzoylfluoroacetate, b. p. 121—130° (13 g.). The ester therefore gave 50% of benzoate plus ethoxalylfluoroacetate, 40% of oxalate plus benzoylfluoroacetate and, probably, 10% of carbonate plus benzoylpyruvate.

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[8] Bergmann, Cohen, and Shahak, *J.*, 1959, 3286.