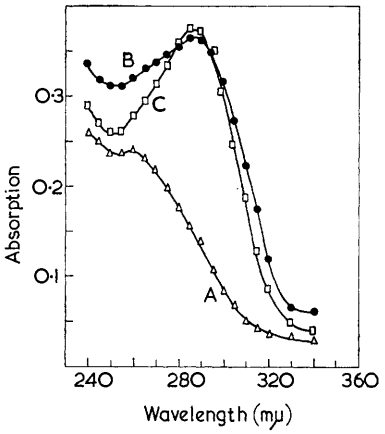
696. *Studies on Organic Fluorine Compounds. Part XXX.* Some Reactions of Fluoropyruvic Acid.*

By Ernst D. Bergmann and A. Mielewitz.

Fluoropyruvic acid reacts with alkanethiols exothermically to give alkylthiopyruvic acids. Ethanolamine replaces both the fluorine atom and the methoxy-group of methyl fluoropyruvate, giving the amino-amide (I). Cysteamine, on the other hand, induces a much more complex reaction, leading to a tricyclic thiazine (V).

Avi-Dor and his colleagues[1] observed that fluoropyruvic acid reacts quickly in biological media with thiol groups, liberating one mol. of hydrofluoric acid. In aqueous solution the products have a characteristic absorption band at 265 mμ, which is shifted to 300 mμ on addition of borate or bivalent cations such as zinc. An analogous observation has been made in the case of 3-indolylpyruvic acid.[2] If the thiol group is part of a system $>C(NH_2)\cdot C(SH)<$, the reaction with fluoropyruvic acid leads directly to a compound absorbing at 300 mμ.

It seemed of interest to study the mechanism of this reaction which has been shown to be of analytical value.[1] Sodium fluoropyruvate and the sodio-derivatives of ethane-, butane-, and toluene-ω-thiol give the salts of the corresponding alkylthiopyruvic acids in



Ultraviolet absorption spectrum of ethylthiopyruvic acid in water (2×10^{-4}M). (A) in 0·10M-"Tris" buffer (pH 8·0); (B), as (A) but containing 2×10^{-3}M-$ZnSO_4$; (C) in 0·50M-borate buffer (pH 8·0).

a strongly exothermic reaction. In view of the strength of the C–F bond, this high reactivity is somewhat surprising; it may be rationalized by assuming that the reaction is in fact an addition of the thiol to the enol form of the fluorinated acid:

$$CHF{=}C(OH)\cdot CO_2H \longrightarrow CHF(SR)\cdot CH(OH)\cdot CO_2H$$

followed by elimination of hydrofluoric acid. Also ethyl chloro- and bromo-pyruvate with ethanethiol give ethyl ethylthiopyruvate.[3] Comparative experiments with sodium fluoroacetate and fluoroacetone have shown that their conversion into butylthioacetic acid and butylthioacetone takes place with reasonable speed only at 100°.

In aqueous solution the three alkylthiopyruvic acids showed an absorption maximum at 265 mμ; in the case of the ethyl compound borate or zinc ions shift the maximum to 300 mμ (see Figure).

* Part XXIX, *Bull. Res. Council Israel*, 1961, **10**, *A*, 91.

[1] Avi-Dor and Mager, *J. Biol. Chem.*, 1956, **222**, 249; Avi-Dor and Lipkin, *ibid.*, 1958, **233**, 69; Avi-Dor, *Biochem. J.*, 1960, **76**, 370; *Biochem. Biophys. Acta*, 1959, **34**, 266; cf. Peters and Hall, *ibid.*, 1957, **26**, 433.

[2] Spencer and Knox, *Arch. Biochim. Biophys.*, 1962, **96**, 115.

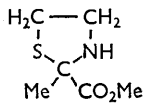
[3] Bonnema, Alkema, and Arens, *Rec. Trav. chim.*, 1960, **79**, 937.

Compounds such as 2-aminoethanethiol (cysteamine) may be expected to react with fluoropyruvic acid according to one of two primary mechanisms, nucleophilic attack on the C–F bond or formation of a thiazolidine ring through the α-keto-group.[4] The reactions of methyl fluoropyruvate with ethanolamine and of the fluorine-free methyl pyruvate with ethanolamine and cysteamine were first studied. In the first of these reactions, the fluorine atom was attacked preferentially; later there was amidation of the ester group: *N*-2-hydroxyethyl-(2-hydroxyethylamino)pyruvamide (I) was formed. This was proved by the analysis of the crystalline product and by the infrared spectrum, which showed the two amide bands at 1530 and 1653 cm.$^{-1}$. Biekert and his co-workers [5] isolated a similar compound as one of the products of the reaction between ethyl phenylglyoxylate and aminoethanol.

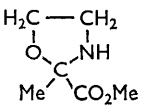
Reaction of methyl pyruvate with ethanolamine gave two products, each having the composition of the oxazolidine (III), and the reaction with cysteamine gave two products having the composition of the thiazolidine (II). The members of each pair differed widely in boiling point. The low-boiling liquids, which were the main products, were undoubtedly the substances (II) and (III). The former showed typical thiazolidine peaks [4] in the infrared spectrum (1080, 1117, 1170, and 1188 cm.$^{-1}$), no C=N absorption, the NH peak at 3330 cm.$^{-1}$, and the normal absorption of a non-conjugated methoxycarbonyl group. In the spectrum of substance (III), the oxazolidine frequencies [6] (1039, 1060, 1093, 1124, and 1156 cm.$^{-1}$) and the C=N absorption (1651 cm.$^{-1}$) were observed, showing an equilibrium with an open form (IIIa) which is somewhat stabilized by conjugation between the C=N and the C=O double bond.[6]

The reaction of ethanolamine with methyl pyruvate thus differs in its mechanism from those with ethyl oxaloacetate or phenylpyruvate which lead to six-membered ring systems, *e.g.*, (IIIb) in the former case.[7]

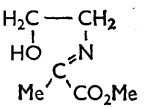
(I) $HO\cdot CH_2\cdot CH_2\cdot NH\cdot CH_2\cdot CO\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot OH$



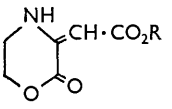
(II)



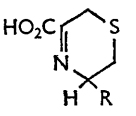
(III)



(IIIa)

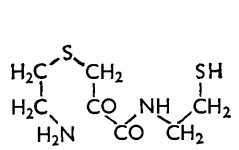


(IIIb)

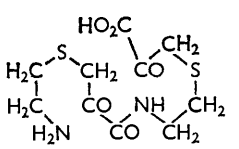


(IV)

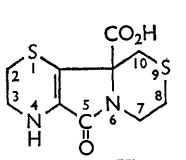
The reaction of fluoropyruvic acid with cysteamine gave products analogous to those obtained from bromopyruvic acid and cysteamine,[8] namely, (IV; R = H) at normal and (V) at elevated temperatures. Formation of the thiazine derivative (IV) requires attack by the thiol group on the C–F bond, followed by loss of water between the keto- and the amino-group. Analogously, cysteine methyl ester gave an ester (IV; R = CO_2Me), which has an absorption band at 296 mμ (log ε 3·74). The product [8a] (V) absorbs at 308



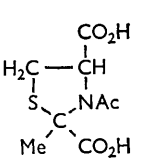
(VI)



(VII)



(V)



(VIII)

mμ (log ε 3·71) and its formation can be rationalized as follows: In analogy to product (I), an amino-amide (VI) is formed, the thiol- and not the amino-group attacking the C–F bond;

[4] See Bergmann and Kaluszyner, *Rec. Trav. Chim.*, 1959, **78**, 289; Njaa, *Nature*, 1961, **192**, 463.
[5] (*a*) Biekert and Sonnenbichler, *Chem. Ber.*, 1961, **94**, 2785; (*b*) Biekert, Sonnenbichler, and Hoffmann, *ibid.*, 1962, **95**, 1451.
[6] Bergmann, *Chem. Rev.*, 1953, **53**, 309.
[7] Bickert, Hoffmann, and Enslein, *Chem. Ber.*, 1961, **94**, 2778.
[8] (*a*) Strukov, *Zhur. obshchei Khim.*, 1958, **28**, 69; (*b*) Hermann, *Chem. Ber.*, 1961, **94**, 442.

this product reacts with a further molecule of fluoropyruvic acid analogously, giving the acid (VII); an aldol reaction and elimination of two mol. of water, followed by tautomerisation of the CH–C=N to the C=C–NH grouping leads eventually to the product (V). It may be recalled that cysteine and pyruvic acid form a thiazolidine, characterized as its acetyl derivative (VIII).[9]

Experimental

Butylthiopyruvic Acid.—To a solution of sodium hydroxide (3·7 g.) in water (10 ml.), butane-1-thiol (4·2 g.). and fluoropyruvic acid[10] (5 g.). in water (10 ml.) were added. The reaction was exothermic, and sodium fluoride was precipitated. After cooling, the mixture was acidified with 20% sulphuric acid and extracted three times with ether (10 ml.). The ethereal layers were dried and concentrated, and the *product* (3·6 g., 37%) recrystallized from benzene; it melted at 129—130° and had $\lambda_{max.}$ (in EtOH) 290 mμ (log ε 4·08), $\nu_{max.}$ (in KBr) 3400 (OH), 1667 (C=O), and 755 (C–S stretch)[11] (Found: C, 47·9; H, 6·7. $C_7H_{12}O_3S$ requires C, 47·7; H, 6·8%).

Ethylthiopyruvic Acid.—Sodium hydroxide (1·60 g.) in water (5 ml.), ethanethiol (1·24 g.), and fluoropyruvic (2·12 g.) acid in water (5 ml.), gave *ethylthiopyruvic acid* (0·2 g., 7%) which, recrystallized from benzene, had m. p. 128—129°, $\lambda_{max.}$ (in EtOH) 212 (log ε 3·60) and 290 mμ (log ε 4·08), $\nu_{max.}$ (in KBr) 3420, 1667, and 760 cm.$^{-1}$ (Found: C, 40·7; H, 5·8. $C_5H_8O_3S$ requires C, 40·5; H, 5·4%). The yield was low owing to the solubility of the product in water.

Benzylthiopyruvic Acid.—To a solution of sodium hydroxide (1·60 g.) in water (5 ml.), toluene-ω-thiol (2·48 g.) and fluoropyruvic acid (2·12 g.) in water (5 ml.) were added. Working-up as above gave a solid (2 g., 50%) which when recrystallized from benzene melted at 125—126° and had $\lambda_{max.}$ (in EtOH) 290 mμ (log ε 4·08), $\nu_{max.}$ (in KBr) 3400, 1667, and 760 cm.$^{-1}$ (Found: C, 57·0; H, 4·8. $C_{10}H_{10}O_3S$ requires C, 57·2; H, 4·8%).

Butylthioacetic Acid.—A mixture of sodium hydroxide (2·66 g.) in water (5 ml.), butanethiol (3 g.), and fluoroacetic acid (2·6 g.) in water (5 ml.) was refluxed for 1 hr., then acidified with 20% sulphuric acid and extracted repeatedly with ether. The product (2 g., 41%) was an oil, b. p. 90—90·5°/0·3 mm., ν(CO) (liquid film) 1717 cm.$^{-1}$ (shoulder at 1730 cm.$^{-1}$), $\lambda_{max.}$ (in EtOH) 245 mμ (log ε 2·54) (Found: C, 48·2; H, 8·0. Calc. for $C_6H_{12}O_2S$: C, 48·6; H, 8·1%). This acid has been prepared before by other methods.[12]

Butylthioacetone.—A solution of sodium hydroxide (0·31 g.), butane-1-thiol (1·18 g.), and fluoroacetone[13] (1·0 g.) in water (10 ml.) was refluxed for 1 hr. and worked up as above. The product (1 g., 52%) had b. p. 61°/1·1 mm., ν(CO) (liquid film) 1717 cm.$^{-1}$ (shoulder 1730 cm.$^{-1}$) and $\lambda_{max.}$ (in EtOH) 216, 244, and 299 mμ (log ε 2·82, 2·52, and 2·42) (Found: C, 57·6; H, 10·0. Calc. for $C_7H_{14}OS$: C, 57·6; H, 9·6%). The last maximum has also been reported for ethyl thioacetone by Bergson and Delin[14] who indicate for the carbonyl absorption a value of 1704·3 (liquid film) and of 1715·6 (in hexane). Butylthioacetone has been prepared before.[15]

N-2-*Hydroxyethyl*-(2-*hydroxyethylamino*)*pyruvamide.*—When methyl fluoropyruvate[16] (7 g.) and ethanolamine (3·55 g.) in benzene (5 ml.) were refluxed under azeotropic conditions, water did not separate. After 3 hr. the solvent was evaporated and the solid residue (2 g., 36%) recrystallized from methanol. The *product*, m. p. 171—172°, was free from fluorine and methoxyl (Found: C, 44·0; H, 7·2; N, 15·7. $C_7H_{14}N_2O_4$ requires C, 44·2; H, 7·4; N, 14·7%) and had $\nu_{max.}$ (in KBr) 3280, 3000, 1667, 1540, 1450, 1316 (and shoulder), 1260, 1220, 1120, 1064, 1047, 1020, 833, and 770 (broad) cm.$^{-1}$.

Methyl 2-Methylthiazolidine-2-carboxylate (II).—Methyl pyruvate (2·3 g.) and cysteamine (1·93 g.) in benzene (15 ml.) were distilled azeotropically until no more water was removed. Distillation of the product gave fractions, (*a*) the *ester* (II), b. p. 45°/0·01 mm. (3 g., 67%), $\lambda_{max.}$

[9] Schubert, *J. Biol. Chem.*, 1936, **114**, 341; 1937, **121**, 539.
[10] Blank, Mager, and Bergmann, *J.*, 1955, 2190; Nair and Busch, *J. Org. Chem.*, 1958, **23**, 137.
[11] Scott and McCullough, *J. Amer. Chem. Soc.*, 1958, **80**, 3554.
[12] Uyeda and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 2385; Mooradian, Cavallito, Bergmann, and Lawson, and Vand Suter, *ibid.*, 1949, **71**, 3372.
[13] Bergmann and Cohen, *J.*, 1958, 2259.
[14] Bergson and Delin, *Arkiv Kemi*, 1961, **18**, 489.
[15] Morey, U.S.P. 2,363,462; Yamomoto, *J. Pharm. Soc. Japan*, 1952, **72**, 1124; Bradsher, Brown, and Grantham, *J. Amer. Chem. Soc.*, 1954, **76**, 114.
[16] Clinton and Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135.

(in EtOH) 250 mμ (infl.; log ε 2·57) (Found: C, 45·0; H, 7·4; N, 8·4; MeO, 18·7. $C_6H_{11}NO_2S$ requires C, 44·6; H, 6·8; N, 8·7; MeO, 18·9%), and (*b*) b. p. 109·5°/0·02 mm. (0·5 g., 11%), $\lambda_{max.}$ (in EtOH) 254 mμ (infl.; log ε 2·54) (Found: C, 44·4; H, 3·0; N, 9·1%). The structure of the by-product has not been elucidated.

Reaction of Methyl Pyruvate and Ethanolamine.—Reaction between methyl pyruvate (15 g.) and ethanolamine (9 g.) in benzene (50 ml.), carried out as in the preceding paragraph, gave fractions, (*a*) b. p. 43°/0·6 mm. (2 g., 8·5%), $\lambda_{max.}$ (in EtOH) 316 (log ε 1·82) (Found: C, 50·6; H, 7·0. $C_6H_{11}NO_3$ requires C, 49·6; H, 7·6%), and (*b*) b. p. 98·5°/0·005 mm. (0·5 g., 2%), $\lambda_{max.}$ (in EtOH) 267 mμ (log ε 2·85) (Found: C, 52·1; H, 7·6%). The structure of fraction (*b*) has not been elucidated. Fraction (*a*) is considered to consist of *methyl 2-methyloxazolidine-2-carboxylate* (III) with some of its open-chain isomer (IIIa).

Reaction of Fluoropyruvic Acid and Cysteamine.—A solution of cysteamine (1·54 g.) and sodium methoxide (1·08 g.) in methanol (20 ml.) was added to fluoropyruvic acid (2·12 g.) in methanol (5 ml.); the mixture was refluxed for 1 hr. and acidified with 10% sulphuric acid. 3,4,5,7,8,10a-*Hexahydro*-5-*oxo*-2H,10H-*pyrrolo*[1,2-*c*:3,4-*b'*]*di*[1,4]*thiazine*-10a-*carboxylic acid* (V) which separated (2·2 g., 81%) crystallised from methanol and melted at 143—144° (decomp.) (Found: C, 44·4; H, 4·5; N, 10·2. $C_{10}H_{12}N_2S_2O_3$ requires C, 44·1; H, 4·4; N, 10·3%). Strukov [8a] gave m. p. 143—144° H; the formula (V) was proposed by Hermann.[8b]

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Department of Organic Chemistry, Hebrew University,
Jerusalem, Israel. [*Received, January 8th,* 1963.]