The product, 188 g., was scrubbed, dried and fractionated. Of the 173 g. charged to the column, 100 g. (58%) of $C_4F_8Br_2$ boiled at 94–95°; there was an additional 25.6 g., b.p. 91–94°; total yield of dibromide, 73%.

The Preparation of $(CF_3)_2CBrCF_2Br$.—9.3 g. of *i*-C_4F_8 (0.047 mole), 5.7 g. of bromine (0.035 mole), 3 drops of water and a few crystals of acetamide were sealed in a Pyrex ampoule. There was no evident reaction in the dark at room temperature, but after three hours of exposure to an ultraviolet lamp, reaction appeared to be complete. The 8 g. of high-boiling products was separated in the vacuum system. There was obtained 4.0 g. (35%) of a white solid identified as the dibromide.[18]

Attempts to brominate *i*-C_4F_8 thermally at 100° or with ultraviolet light at room temperature in the absence of acetamide were unsuccessful.

The Preparation of $CF_3CFBrCFBrCF_3$.—The C_4F_8-2 used for the preparation of the dibromide was contained in intercuts from a series of *i*-C_4F_8 preparations. The amount of C_4F_8-2 in each fraction was determined by infrared analysis; the fraction was sealed up with slightly more than enough bromine to convert all of the C_4F_8-2 to dibromide and exposed to ultraviolet light until no further reaction was observed. Bromination was found to be rapid and quantitative; the recovered *i*-C_4F_8 did not contain any C_4F_8-2 and the C_4F_8-2 later recovered from the dibromide did not contain *i*-C_4F_8. After bromination of C_4F_8-2 the unreacted *i*-C_4F_8 was boiled off and collected, and mercury was added to the dibromide to remove excess bromine. The products from the various dibromide preparations were collected and fractionated.

The Debromination of $CF_3CFBrCFBrCF_3$.—$C_4F_8Br_2$ from the preparation described above was used; it had b.p. 96°, $n^{25}D$ 1.3538. Fifty-two grams of the dibromide was added slowly to a mixture of 200 cc. of boiling glacial acetic acid and 20 g. of zinc dust; the mixture was refluxed for about three hours. The volatile product, C_4F_8-2, was collected in a liquid air-cooled trap; yield 33 g. The olefin was separated from a small amount of entrained acetic acid by distillation in the vacuum system. The infrared spectrogram of this sample of C_4F_8-2 was quite similar to those of samples of C_4F_8-2 from pyrolytic reactions.

A larger quantity of C_4F_8-2 was prepared by the same process, treated with KOH and P_2O_5, and fractionated; the product was virtually the same as the C_4F_8-2 that had not been base treated, indicating that neither the base nor P_2O_5 changed the *cis–trans* ratio. This point is of interest since nearly all of the pyrolytic C_4F_8-2 had been treated with these reagents.

The Addition of Ethanol to *i*-C_4F_8.—A glass bubbler was charged with 65 g. (1.4 moles) of ethanol. The reactor was kept at about 9° while 50 g. (0.24 mole) of *i*-C_4F_8 was bubbled into the reactor. The reaction mixture was poured over ice and the water-insoluble layer separated and dried over $CaSO_4$ and CaO.

The crude ether, 54 g., was fractionated and 25 g. of $(CF_3)_2CHCF_2OC_2H_5$ obtained. This is a 41% yield based on the *i*-C_4F_8; b.p. 83° at 743 mm., $n^{25}D$ 1.2908, d^{25}_4 1.3946, γ^{25} 16.3 dynes/cm. *Anal.* Calcd. for $C_6F_8H_6O$: C, 29.3; F, 61.7. Found: C, 29.6; F, 60.4.

The Attempted Alkaline Oxidation of *i*-C_4F_8.—The attempted alkaline oxidation of *i*-C_4F_8 gave neither hexafluoroacetone nor the expected cleavage product CF_3H. Instead, $(CF_3)_3CH$ was produced. It was considered to result from the addition of HF to *i*-C_4F_8; the decomposition of some of the *i*-C_4F_8 must occur to furnish the necessary HF.

A mixture of 80 g. of $KMnO_4$ (0.51 mole), 50 g. of KOH (0.9 mole), 100 g. of *i*-C_4F_8 (0.5 mole) and 300 cc. of water was sealed in glass ampoules and heated at 90° overnight. The ampoules were opened and the volatile products charged to a low temperature fractionating column. There was no material boiling below about 0°. There was isolated 12.6 g., b.p. +11 to +12°, mol. wt., 216–218. *Anal.* Calcd. for C_4F_9H: mol. wt., 220; F, 77.7; C, 21.9. Found: F, 76.3; C, 22.3. The boiling point is about the same as that of its isomer $CF_3CF_2CF_2CF_2H$ which is 14° at 740 mm. Infrared analysis showed that there was virtually no *i*-C_4F_8 left and no other compounds containing C=C or C=O groups. The spectrogram matched that of the compound prepared by the direct addition of HF to *i*-C_4F_8.

The direction of addition is assumed to be the same as that of HX to other fluorocarbon olefins.

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(18) The addition of acetamide and water to the bromine to provide a more powerful brominating mixture was suggested by Dr. J. D. Park of the University of Colorado.

[CONTRIBUTION NO. 578 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. V. Alkamine Esters of Phenyl-3-thienylglycolic Acid[1]

BY E. CAMPAIGNE AND R. C. BOURGEOIS[2]

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Phenyl-3-thienylglycolic acid has been synthesized *via* a benzilic acid rearrangement of benz-3-thenil, which was obtained from the product of a mixed benzoin condensation of benzaldehyde and 3-thenaldehyde. This product was shown to be phenyl-3-thenoylcarbinol by rearrangement of the oxime. During the course of the investigation, 3-thienylglycolic acid and 3,3′-thenil were prepared. 3,3′-Thenilic acid proved too unstable to characterize well. The alkamine esters of phenyl-3-thienylglycolic acid have approximately the same antispasmodic activity as the corresponding 2-thienyl isomers.

In continuing studies on the comparison of the properties of physiologically active 2- and 3-thienyl isomers,[3] attention was turned to the alkamine esters of phenylthienylglycolic acid, the 2-isomers of which have been shown[4] to be potent substitutes for the clinically useful antispasmodic drug, Trasentin (β-diethylaminoethyl diphenylacetate).

Blicke and Tsao[5] prepared phenyl-2-thienylglycolic acid in two ways: by the reaction of phenylmagnesium bromide with 2-thienylglyoxylic acid, and by the reaction of 2-thienylmagnesium bromide on phenylglyoxylic acid. Neither of these methods can be readily applied in the 3-thiophene series because of the difficulty of obtaining the appropriate substitutions in the 3-position. Several attempts were made to obtain 3-thienylglyoxylic acid. Efforts to oxidize 3-acetothienone led only

(1) Taken in part from the Thesis submitted by R. C. B. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, June, 1951.

(2) Sterling-Winthrop Fellow in Chemistry, 1950–1951.

(3) For previous papers in this series see R. G. Garst, E. Campaigne and H. G. Day, *J. Biol. Chem.*, **180**, 1013 (1949); or E. Campaigne and W. M. LeSuer, THIS JOURNAL, **71**, 333 (1949).

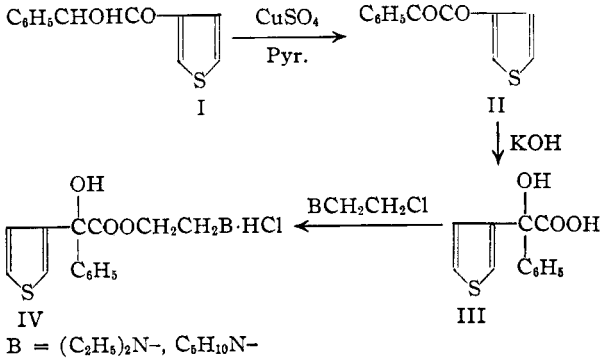
(4) *Cf.* (a) F. A. Lands, V. Nash and K. Hooper, *J. Pharm. Exp. Ther.*, **86**, 129 (1946); (b) R. F. Feldkamp and J. A. Faust, THIS JOURNAL, **71**, 4012 (1949).

(5) F. F. Blicke and M. Tsao, *ibid.*, **66**, 1645 (1944).

to 3-thenoic acid and decomposition products, although it had been reported[6] that 2-acetothienone may be oxidized to 2-thienylglyoxylic acid in good yield. Attempts to prepare 3-thenoyl cyanide, which might be hydrolyzed to the desired acid,[7] resulted only in brittle black polymers. Acree[8] oxidized mandelic acid to phenylglyoxylic acid, so a sample of 3-thienylglycolic acid was synthesized by hydrolysis of the cyanohydrin in dilute acid. However, the desired oxidation of the carbinol to ketone could not be effected.

The synthesis of phenyl-3-thienylglycolic acid (III) was ultimately accomplished by way of a mixed benzoin condensation, followed by oxidation to benz-3-thenil (II) and rearrangement. Benzaldehyde and 3-thenaldehyde readily condensed together under the usual benzoin condensation conditions to give a pure product which analyzed correctly for a mixed benzoin,[9] either phenyl-3-thenoylcarbinol (I) or 3-thienylbenzoylcarbinol, either of which could have been used. A Beckmann Rearrangement of the oxime gave benzaldehyde, identified by its 2,4-dinitrophenylhydrazone, and 3-cyanothiophene, identified by conversion to the known 3-thenamide, which proved the correct structure of the oxime to be *syn*-3-thienyl α-hydroxybenzyl ketoxime[10] and the benzoin to be I.

I was oxidized to the corresponding diketone, benz-3-thenil (II), with copper sulfate in pyridine. II readily formed a quinoxaline with *o*-phenylenediamine, and underwent the benzilic acid rearrangement in aqueous alcoholic potassium hydroxide to form phenyl-3-thienylglycolic acid (III). The basic alkyl esters were formed by refluxing III with the appropriate basic alkyl chlorides in isopropyl alcohol. Horenstein and Pahlicke[11] prepared basic alkyl ester hydrochlorides by fusing equivalent



B = $(C_2H_5)_2N$–, $C_5H_{10}N$–

amounts of the potassium salt of the acid with the basic alkyl chloride hydrochloride. Since the potassium phenyl-3-thienylglycolate was obtained in good yield directly from the benzthenil rearrangement, this seemed to be a practical approach. However, the products were quite impure and required extensive recrystallization, so that even though the yield of pure acid was quite low (32%), still better yields of the basic esters were obtained from the acid and basic alkyl halide reaction.

Cardon and Lankelma[12] found that 2,2′-thenilic acid could be obtained by rearrangement of 2,2′-thenil, but was quite unstable. The isomeric 3,3′-thenilic acid was therefore prepared, and found to behave similarly. 3,3′-Thenoin was oxidized to 3,3′-thenil, a stable diketone which readily formed 2,3-bis-(3-thienyl)-quinoxaline. The thenil rearranged in alkaline solution, but the resultant acid decomposed on standing in a vacuum desiccator.

Preliminary pharmacological tests showed that β-diethylaminoethyl phenyl-3-thienylglycolate hydrochloride exhibited approximately 63% of the antispasmodic activity of atropine sulfate, while in a parallel experiment the 2-thienyl isomer gave about 85%. Activities of the other derivatives were of the same order. From this one can conclude that the antispasmodic activities of the two isomers are identical within experimental error. A similar relationship between the dialkylaminoalkyl esters of the isomeric thenoic acids had been observed previously.[13]

Acknowledgment.—We are indebted to the Sterling-Winthrop Research Institute for the pharmacological testing of these compounds, and for the Fellowship in support of this research.

Experimental[14]

3-Thienylglycolic Acid.[15]—A solution of 5.0 g. (0.12 mole) of sodium cyanide in 25 ml. of water and 10 g. (0.09 mole) of 3-thenaldehyde[16] was placed in a 200-ml. wide-mouthed bottle fitted with a stirrer. Stirring was started and 28 ml. of saturated sodium bisulfite solution was slowly added. About 28 g. of chipped ice was added in portions at the same time. Approximately 5 minutes after the addition was complete, the yellow 3-thenaldehyde cyanohydrin was separated from the aqueous layer in a separatory funnel, added to 25 ml. of 9 *N* hydrochloric acid in a 200-ml. flask and shaken vigorously for 12 hours. The acidic solution was extracted with three 50-ml. portions of ether, the ether dried and removed on a steam-bath. The residual oil was taken up in hot benzene, which on cooling deposited colorless plates. A second recrystallization gave 3.2 g. (22%) of 3-thienylglycolic acid, melting at 107–108°.

Anal. Calcd. for $C_6H_6O_3S$: S, 20.27; neut. equiv., 158. Found: S, 20.45; neut. equiv., 158.

Phenyl-3-thenoylcarbinol (I).—Freshly distilled 3-thenaldehyde (32 g., 0.28 mole) and 29.8 g. (0.28 mole) of freshly distilled benzaldehyde were dissolved in 240 ml. of 95% ethanol, a solution of 6 g. of potassium cyanide in 60 ml. of water was added, and the mixture refluxed for one hour. After cooling and recrystallization from ethanol, 35 g. (58%) of white needles were obtained, which melted at 113–114°.

Anal. Calcd. for $C_{12}H_{10}O_2S$: S, 14.68. Found: S, 14.42.

The oxime was prepared by refluxing I with hydroxylamine in a mixture of pyridine and anhydrous alcohol for ten hours. After removal of the solvents the residue was shaken with water and allowed to crystallize. The oxime was recrystallized twice from benzene to yield a white powder, melting at 139–140°.

Anal. Calcd. for $C_{12}H_{11}O_2NS$: S, 13.74. Found: S, 13.40.

(6) R. F. Feldkamp, private communication.

(7) K. Buchka, *Ber.*, **20**, 395 (1887).

(8) S. F. Acree, *Am. Chem. J.*, **50**, 391 (1913).

(9) During the time this work was in progress, it was learned that Professor H. P. Lankelma and S. Cardon, of Western Reserve University, had accomplished this same condensation. We are grateful to them for a sample of the mixed benzoin which proved to be identical with our compound.

(10) W. S. Ide and J. S. Buck, "Org. Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 279.

(11) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1654 (1938).

(12) S. Z. Cardon and H. P. Lankelma, THIS JOURNAL, **70**, 4248 (1948).

(13) E. Campaigne and W. M. LeSuer, *ibid.*, **70**, 3498 (1948).

(14) All melting points are uncorrected.

(15) W. M. LeSuer, Ph.D. Thesis, Indiana University, 1948.

(16) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

Beckmann Rearrangement of Phenyl-3-thenoylcarbinol Oxime.—Phenyl-3-thenoylcarbinol oxime (13 g.) was dissolved in 150 ml. of water containing 5 g. of sodium hydroxide. To this solution was added in portions with shaking 30 g. of benzenesulfonyl chloride. The temperature was not allowed to rise more than a few degrees and care was taken to keep the mixture alkaline. After all the chloride had disappeared the oily layer was thoroughly extracted with ether and the ether solution dried over anhydrous sodium sulfate. After removal of the ether, the residual oil was vacuum distilled (10 mm.) and the first fraction yielded an aldehyde, the 2,4-dinitrophenylhydrazine derivative of which melted at 236–237° and did not depress the melting point of authentic benzaldehyde-2,4-dinitrophenylhydrazone. Acid hydrolysis of the remaining fraction gave an amide melting at 178–179° which did not depress the melting point of 3-thenamide.[16]

Benz-3-thenil (II).—This compound was obtained by the method of Hartman and Dickey.[17] A mixture of 61 g. (0.24 mole) of crystalline copper sulfate, 59 g. of pyridine and 27 ml. of water was heated with stirring until all the copper sulfate had dissolved. To this solution was added 26.5 g. (0.12 mole) of phenyl-3-thenoylcarbinol and the mixture heated and stirred for two hours. The mixture was then poured into water and allowed to cool. Filtration and recrystallization from methanol yielded 16.5 g. (63%) of pale yellow crystals, melting at 81–82°.

Anal. Calcd. for $C_{12}H_8O_2S$: S, 14.77. Found: S, 14.56.

The quinoxaline derivative was prepared by refluxing for 2 hours 1.0 g. of the diketone with 0.84 g. of *o*-phenylenediamine dihydrochloride in ethanol. After recrystallization from ethanol the 2-phenyl-3-(3-thienyl)-quinoxaline melted from 131–132°.

Anal. Calcd. for $C_{18}H_{12}N_2S$: S, 11.10. Found: S, 10.92.

Phenyl-3-thienylglycolic Acid (III).—To a solution of 20 g. of potassium hydroxide in 80 ml. of 50% alcohol was added 20 g. (0.082 mole) of benz-3-thenil and the mixture refluxed for ten minutes on a steam-bath. The resulting deep purple solution was poured into a crystallizing dish and allowed to stand overnight during which time 22 g. of the potassium salt of the acid crystallized. The salt was collected and dissolved in 1 ml. of concentrated hydrochloric acid in 200 ml. of water. The dark brown, gummy precipitate was removed and the nearly colorless filtrate was acidified with concentrated hydrochloric acid to precipitate the acid. Recrystallization from water yielded 7 g. (32.5%) of white crystals melting at 134–135°.

Anal. Calcd. for $C_{12}H_{10}O_3S$: S, 13.67; neut. equiv., 234. Found: S, 13.42; neut. equiv., 235.

β-Diethylaminoethyl Phenyl-3-thienylglycolate Hydrochloride.—Crude β-diethylaminoethyl chloride was prepared by ether extraction of a bicarbonate-neutralized aqueous solution of β-diethylaminoethyl chloride hydrochloride.[18] A solution of 3.15 g. (0.015 mole) of III and 2.2 g. of the crude basic chloride in 20 ml. of dry isopropyl alcohol was refluxed for 17 hours. The alcohol was then removed under reduced pressure until the salt crystallized. It was dissolved in absolute ethanol and reprecipitated with anhydrous ether, giving 4.5 g. (81%) of a white crystalline salt melting at 159–160°.

Anal. Calcd. for $C_{18}H_{24}O_3NSCl$: N, 3.79; S, 8.65. Found: N, 3.51; S, 8.42.

The methobromide was prepared by treating the crude free base of the ester with excess methyl bromide in anhydrous ethanol for 24 hours. After concentrating the alcohol solution, absolute ether was added to precipitate the methobromide. The white quaternary salt, melting at 140–143°, was obtained in 80% yield.

Anal. Calcd. for $C_{19}H_{26}O_3NSBr$: N, 3.27; S, 7.48. Found: N, 3.58; S, 7.40.

N-β-Piperidinoethyl Phenyl-3-thienylglycolate Hydrochloride.[19]—This ester hydrochloride was prepared from N-β-piperidinoethyl chloride as previously described. From 4.6 g. (0.019 mole) of the acid there was obtained 6 g. (80%) of the recrystallized hydrochloride melting at 165–167°.

Anal. Calcd. for $C_{19}H_{24}O_3NSCl$: N, 3.67; S, 8.39. Found: N, 3.78; S, 8.26.

From 2.5 g. of the free basic ester, 2.7 g. (84%) of crystalline methobromide melting at 192–195° was obtained.

Anal. Calcd. for $C_{20}H_{26}O_3NSBr$: N, 3.18; S, 7.28. Found: N, 3.31; S, 7.26.

3,3′-Thenil.—A solution of 7.5 g. of copper sulfate pentahydrate in 10 ml. of pyridine and 5 ml. of water was heated on a steam cone and 3.0 g. (0.013 mole) of 3,3′-thenoin[16] was added. The mixture was heated and stirred for two hours, and then poured into 150 ml. of water. By recrystallizing the yellow precipitate from methanol, 2.5 g. (83%) of 3,3′-thenil, melting at 75–76°, was obtained.

Anal. Calcd. for $C_{10}H_6O_2S_2$: S, 28.88. Found: S, 28.59.

2,3-Bis-(3-thienyl)-quinoxaline was obtained as white needles from ethanol, melting at 134–135°.

Anal. Calcd. for $C_{16}H_{10}N_2S_2$: S, 21.77. Found: S, 21.60.

3,3′-Thenilic Acid.—A mixture of 5 g. of potassium hydroxide in 20 ml. of 50% ethanol was refluxed with 5 g. of 3,3′-thenil for 15 minutes, and then let stand overnight. A tarry precipitate formed on careful neutralization with hydrochloric acid to congo red paper. After filtering, the clear filtrate was extracted with ether, and the ether extract concentrated. Grayish crystals were obtained which darkened immediately, and decomposed on storing overnight in a vacuum desiccator. The compound decomposed with charring below 90°.

Anal. Calcd. for $C_{10}H_8O_3S_2$: neut. equiv., 240. Found: neut. equiv., 236.

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(17) W. W. Hartman and J. B. Dickey, THIS JOURNAL, **55**, 1228 (1933).

(18) G. A. Gough and H. King, *J. Chem. Soc.*, 2436 (1928).

(19) Through an error, the structural formula of this compound is written for the 2-isomer in an article by R. W. Pickering, B. E. Abreu, J. Chen, R. C. Burnett and W. C. Bostick, *J. Pharm. Exp. Ther.*, **95**, 122 (1949).