TABLE I

FORMATION OF ARYL ISOTHIOCYANATES BY THE MODIFIED KALUZA SYNTHESIS

IV	Structure	Time for dithiocarbamate formation	Yield of II, %	Yield of IV, %	B.p., °C. (mm.)	M.p., °C.	M.p. of aniline derivative Lit.	M.p. of aniline derivative Found
a	C_6H_5NCS	24 hr.	90	81	105–108 (14)		154[a]	153
b	o-CH_3—C_6H_4NCS	24 hr.	89	80	126–129 (12)		136[b]	136
c	m-CH_3—C_6H_4NCS	24 hr.	94	78	129–132 (12)		94[b]	99
d	p-CH_3—C_6H_4NCS	24 hr.	92	81	130–133 (25)		141[b]	140
e	p-Cl—C_6H_4NCS	72 hr.	83	70		46.5	152[b]	152
f	p-Br—C_6H_4NCS	3–4 days	88	73		50	148[b]	155[c]
g	o-CH_3O—C_6H_4NCS	3 hr.	88	82	156–158 (24)		136[b]	131
h	p-C_2H_5O—C_6H_4NCS	3 hr.	89	88		53–54	136[b]	135
i	p-$(CH_3)_2N$—C_6H_4NCS	15 min.	95	60[d]		69	...	149[e]
j	β-$C_{10}H_7NCS$	7 days	90	73		58–59	129	155[f]
k	p-CH_3O—C_6H_4NCS	3 hr.	95	92	167–168 (18)		143[g]	141
l	p-CN—C_6H_4NCS	None	0	...	...		...	...
m	p-NO_2—C_6H_4NCS	None	0	...	...		...	...

[a] H. S. Fry, *J. Am. Chem. Soc.*, **35**, 1544 (1913). [b] T. Otterbacher and F. C. Whitmore, *ibid.*, **51**, 1909 (1929). [c] *Anal.* Calcd. for $C_{13}H_{11}BrN_2S$: C, 50.49; H, 3.61; N, 9.11. Found: C, 51.08; H, 3.51; N, 9.03. [d] This is the only entry in the table based on a single reaction. The reason for the low yield is probably due to the fact that the product was washed with acid and water (see Experimental). [e] *Anal.* Calcd. for $C_{15}H_{17}N_3S$: C, 66.38; H, 6.32; N, 15.48. Found: C, 66.37; H, 6.31; N, 15.37. [f] *Anal.* Calcd. for $C_{17}H_{14}N_2S$: C, 73.35; H, 5.16; N, 10.25. Found: C, 73.28; H, 5.09; N, 10.20. [g] K. N. Campbell, B. K. Campbell, and S. J. Patelski, *Proc. Indiana Acad. Sci.*, **53**, 119 (1943).

possible to prepare the dithiocarbamate derivatives of these two amines by first forming the lithium compounds before treatment with carbon disulfide, but this has not been investigated.

Carboethoxylation of the aryldithiocarbamate salts was accomplished in chloroform solution without difficulty. The decomposition of the intermediate carboethoxy aryldithiocarbamates was carried out in the same solution with triethylamine. This last reaction seemed much easier than with the aliphatic derivatives, probably because of the higher acid strength of the aromatic compounds. In some of the reactions it was observed that the mustard oils contained (infrared spectra) traces of phenylurethan or diphenylurea derivatives; this could usually be traced to the use of wet chloroform or to improper distillation of the final product. The yields of isothiocyanates ranged from 70 to 90%. Our results with various aromatic amines are summarized in Table I. The aniline derivatives were used for characterization. If the melting point of the aniline derivative differed significantly from the literature value or could not be found, the derivative was analyzed.

Thus, the modified Kaluza method is applicable to aromatic amines[3] with base strengthening, mild base weakening, and no substituents. The method is not applicable, in its present form, to the synthesis of isothiocyanates containing strong electron-withdrawing groups. The synthesis is slower for phenyl isothiocyanate than the generally accepted method, but the use of lead and a steam distillation procedure is avoided.[4] The present method seems more generally applicable than decomposition of thiourea derivatives,[5] does not employ phosgene[6] or thiophosgene,[7] and, overall, gives better yields than any available synthesis.

(3) The original Kaluza synthesis is not applicable to aromatic amines; see ref. 1.

(4) F. B. Dains, R. Q. Brewster, and C. P. Olander, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 447.

(5) F. Cymerman-Craig, M. Moyle, and R. A. White, *Org. Syn.*, **36**, 56 (1956).

(6) V. H. Slotta and H. Dressler, *Ber.*, **63**, 888 (1930).

(7) G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924). This procedure has been modified and employed extensively in the aliphatic series [A. Kjaer, F. Marcus, and J. Conti, *Acta Chem. Scand.*, **7**, 1370 (1953), and later articles].

Experimental

The following is the generalized procedure used for the preparation of all the aryl isothiocyanates. In Table I is shown the times required for salt formation and the melting or boiling point of the various isothiocyanates.

The amine (0.1 mole) was dissolved in the minimum amount of benzene and treated with 6.6 ml. (0.1 mole) of carbon disulfide and 14 ml. of (0.1 mole) of triethylamine, and the solution was cooled to 0°. After complete precipitation of the triethylammonium dithiocarbamate salt (see times in Table I), the solution was filtered; the solid was washed with anhydrous ether and air-dried for about 10 min. The salt was then dissolved in about 75 ml. of chloroform, treated with 14 ml. of triethylamine, and cooled again to 0°. To this solution was added 10.2 ml. (0.1 mole) of ethyl chlorocarbonate dropwise over a 15-min. period with hand stirring. The resulting solution was stirred at 0° for 10 min. and allowed to warm to room temperature during a 1-hr. period. The chloroform solution was washed with 3 *M* HCl and twice with water and was dried over sodium sulfate. The chloroform was evaporated *in vacuo* and the aryl isothiocyanate was either distilled or recrystallized from ethanol depending on the physical state of the compound.

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The Solvolysis of Acid Chlorides with *t*-Alkyl Hydroperoxides[1]

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We have shown recently[3] that *t*-alkyl and *t*-aralkyl chlorides undergo solvolysis with *t*-alkyl hydroperox-

(1) Paper XXXV on Organic Peroxides.

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(3) Paper XXXIV on Organic Peroxides: N. A. Milas, R. J. Klein, and D. G. Orphanos, *Chem. Ind.* (London), 423 (1964).

ides to form in substantial yields di-*t*-alkyl or mixed *t*-alkyl aralkyl peroxides, provided that the hydrogen chloride formed is rapidly removed not by a base,[4] usually incorporated with the reactants, but by a vacuum in rotary evaporators. It is therefore self-evident that the above method can easily be extended to the solvolysis of acid chlorides with *t*-alkyl hydroperoxides, the subject of the present Note. This method not only obviates the need for using a base and its subsequent removal from the reaction products but it also leads to relatively high yields of peroxy esters and in some cases[5] to the formation of new types of peroxides not usually formed in the presence of a base. The experimental conditions described below are optimum for the yields reported.

Experimental

***t*-Butyl Peroxybenzoate.**—Benzoyl chloride was mixed in a round-bottomed ground-joined flask with a large excess of 99.2% *t*-butyl hydroperoxide[6] and the flask was attached to a rotary vacuum (60–70 mm.) evaporator. The reaction was initially exothermic with a rapid evolution of gas. It was then allowed to proceed for 24 hr. with occasional heating to 50–60° to complete the reaction, and then it was subjected to a vacuum of 2 mm. for several hours to remove the excess *t*-butyl hydroperoxide. A colorless residue was obtained which was nearly pure *t*-butyl peroxybenzoate contaminated with traces of benzoic acid. When an infrared spectrum of the residue was taken 10% in carbon tetrachloride and the intensity of the band at 1760 cm.$^{-1}$ compared with that of the infrared spectrum of an authentic sample of *t*-butyl peroxybenzoate, the estimated yield was nearly quantitative.

Di-*t*-butyl Diperoxysuccinate.—Succinyl chloride (5 g.) was mixed with 12 g. of 99.2% *t*-butyl hydroperoxide. The reaction was exothermic and had to be cooled under running cold water. As soon as the reaction subsided (3–4 min.) the flask was attached to a rotary vacuum (60–70 mm.) evaporator. A rapid evolution of gas took place and the reaction mixture almost solidified. In order to complete the reaction it was essential to heat it to 50–60° for 3 hr. longer under reduced pressure (60–70 mm.). Finally, the mixture was cooled to room temperature and dissolved in ethyl ether; the ethereal solution was shaken with a solution of sodium bicarbonate, dried with magnesium sulfate, and filtered; and the ether was removed *in vacuo*. A white cotton-like substance was obtained, yield 6.01 g. (71.2%), m.p. 53–54° (lit.[4a] m.p. 53–54°).

Di-*t*-butyl Diperoxyadipate.—Adipyl chloride (3 g.) was mixed with 9 g. of 99.2% *t*-butyl hydroperoxide. An exothermic reaction also occurred and had to be cooled as before. The mixture was treated and worked up in exactly the same manner as in the preceding case. Di-*t*-butyl diperoxyadipate was obtained as colorless needles, 4.06 g. (85.3%), m.p. 42–43° (lit.[4a] m.p. 42–45°).

Di-*t*-butyl Diperoxyazelate.—Azelayl chloride (5 g.) was mixed with 12 g. of 99.2% *t*-butyl hydroperoxide. A strong exothermic reaction took place and the mixture had to be cooled in cold running water so that the temperature was not allowed to rise above 35°. The reaction mixture became greenish yellow and when the reaction subsided (3–4 min.) the flask was attached to the rotary vacuum (60–70 mm.) evaporator and heated as before for 3 hr. at 50–60° to complete the reaction. The product was worked up as in the previous cases but it was obtained as a viscous oil which could not be crystallized, n^{22}D 1.4451, yield 6.9 g. (94.5%). The infrared spectrum showed two prominent bands at 1780 and 852 cm.$^{-1}$, respectively attributed to the *t*-butyl peroxy ester groups. Since this peroxy ester is new, it was subjected to elementary analysis. The active oxygen was determined by the method of Silbert and Swern.[7]

Anal. Calcd. for $C_{17}H_{32}O_6$: C, 61.42; H, 9.73; (O), 9.63. Found: C, 61.19; H, 9.75; (O), 9.63.

D-*t*-butyl Diperoxysebacate.—Sebacyl chloride (4.8 g.), precooled to 0°, was mixed with 10 g. of 99.2% *t*-butyl hydroperoxide. The reaction, as in the previous case, was highly exothermic and had to be cooled for a short time to about 35°. When the reaction had subsided (3–4 min.) the flask was attached to the rotary vacuum (60–70 mm.) and heated for 3 hr. at 50–60°. The reaction mixture was then worked up as in the previous cases. A colorless viscous oil, 6.5 g. (93.3%), n^{24}D 1.4454, was obtained which failed to crystallize. The infrared spectrum showed two prominent bands at 1780 and 852 cm.$^{-1}$, respectively attributed to the *t*-butyl peroxy ester groups. Since this peroxy ester was also a new product, it had to be analyzed.

Anal. Calcd. for $C_{13}H_{34}O_6$: C, 62.39; H, 9.89; (O), 9.24. Found: C, 62.15; H, 9.90; (O), 9.19.

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(5) Unpublished results of the authors.

(6) Kindly supplied by the Lucidol Division of Wallace and Tiernan, Inc., Buffalo, N. Y.

(7) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

Solid Phase Peptide Synthesis. IV. The Synthesis of Methionyl-lysyl-bradykinin[1]

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A new plasma kinin was isolated recently by Elliott, *et al.*,[2] and identified by them as methionyl-lysyl-bradykinin. This undecapeptide was derived from ox blood by incubation of the pseudo-globulin fraction at pH 7.5, and was purified by ion-exchange chromatography. In continuation of our recent studies on solid phase peptide synthesis[3-6] the synthesis of this new biologically active peptide was undertaken. It was of interest, not only because of its kinin activity, but also because it contained two amino acids, lysine and methionine, which had not previously been introduced into peptides by the new method. In addition, it provided a test of the applicability of the method to the synthesis of a peptide containing eleven amino acid residues, which was longer than had been attempted before. While this work was in progress, a synthesis by classical methods was reported by Schröder.[7] The chemical and biological properties of the peptides made by the two different methods appear to be similar.

The synthesis followed exactly the general method described for the solid phase synthesis of bradykinin.[5,6] *t*-BOC-nitro-L-arginyl-L-prolyl-L-prolyl-glycyl-L-phenylalanyl-O-benzyl-L-seryl-L-prolyl-L-phenylalanyl-nitro-L-arginyl–copolystyrene–2% divinylben-

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