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DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
TECHNOLOGY CENTER
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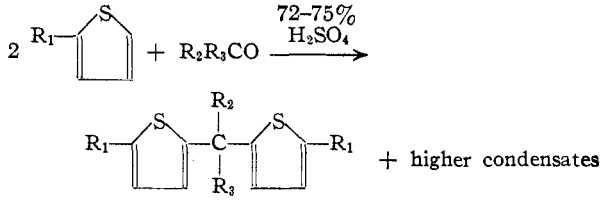
Condensation of Thiophene and Homologs with Ketones

BY JOHN W. SCHICK AND DUNCAN J. CROWLEY

The reaction of thiophene with aldehydes,[1] particularly formaldehyde,[2] in an acidic medium is known to produce 1,1-(2′,2″-dithienyl)-alkanes which on further reaction result in resins and sub-resinous oils. However, no description of the reaction of thiophene and/or substituted thiophenes with ketones has been found in the literature.

The condensation is illustrated in the equation



R_1 = H–, Cl–, CH_3–, R_2 = CH_3–
R_3 = CH_3–, C_4H_3S–, C_6H_5–, C_2H_5–
$R_2R_3C<$ may be cyclic, *e.g.*, in cyclohexanone

This condensation has been carried out with thiophene, 2-methylthiophene and 2-chlorothiophene with ketones, such as acetone, methyl ethyl ketone, cyclohexanone, acetophenone and 2-acetylthiophene. For this particular reaction, the conditions are somewhat similar to those described for the phenol–ketone condensations.[3,4,5,6,7]

Although 72–75% sulfuric acid was the principal condensing agent employed, it was noted that 37% hydrochloric acid resulted in product yields comparable to sulfuric acid, while 85% phosphoric acid resulted in poorer yields. Table I summarizes the experimental data using 72% sulfuric acid as the condensing agent.

General Experimental Conditions

Thiophene or substituted thiophene (0.8–2.0 moles) and the ketone (1.0 mole) were allowed to react in the presence of 72–75% sulfuric acid (acid–thiophene ratio 1.5:1) at 50–90° for 3–8 hours. The reaction product was separated from the acid layer and washed with water, dilute carbonate, water again, then dried over anhydrous sodium sulfate. The unreacted thiophene or substituted thiophene was removed and the residue distilled at reduced pressure.

TABLE I

THIOPHENE–KETONE CONDENSATIONS[a]

Thiophene	Ketone	Mole ratio, thiophene: ketone	Product structure[b]	Formula	Yield,[c] %	B.p., °C.	B.p., Mm.	$n^{20}D$	Sulfur, % Calcd.	Sulfur, % Found
Thiophene	Acetone	1.6	T–K–T	$C_{11}H_{12}S_2$	47	86	0.3	1.5855	30.8	30.9
			T–K–T–K–T	$C_{18}H_{20}S_3$	19	188	.3	1.6029	28.9	28.9
Thiophene	Methyl ethyl	2	T–K–T	$C_{12}H_{14}S_2$	66	97.5	.1	1.5806	28.8	29.0
			T–K–T–K–T[d]	$C_{20}H_{24}S_3$	8				26.6	25.9
			T–K–T_4–K–T[e]	$C_{44}H_{54}S_6$	11	...	[f]		24.8	24.3
Thiophene	Cyclohexanone	1.6	T–K–T[g]	$C_{14}H_{16}S_2$	39	158	.3		25.8	25.7
			T–K–T_2–K–T	$C_{34}H_{40}S_4$	45	...	[f]		22.3	22.4
Thiophene	Acetophenone	1.6	T–K–T	$C_{16}H_{14}S_2$	49	153	.5	1.6319	23.7	23.6
			T–K–T_2–K–T[h]	$C_{40}H_{34}S_4$	30	...	[f]		19.9	20.2
Thiophene	Acetylthiophene	1.6	T–K–T	$C_{14}H_{12}S_3$	54	164	.1	1.6399	34.8	34.6
2-Chlorothiophene	Acetone	0.8	T–K–T	$C_{11}H_{10}S_2Cl_2$	61	143	.5		23.1	22.7
2-Methylthiophene	Acetone	1.6	T–K–T	$C_{13}H_{16}S_2$	79	110	.5	1.5691	27.1	26.5

[a] Condensation carried out in 72–75% H_2SO_4 with an acid:thiophene mole ratio of 1.5:1. [b] T = thiophene, K = ketone. [c] Yield based on thiophene consumed. [d] Mol. wt., calcd. 360, found 376. [e] Mol. wt., calcd. 774, found 772. [f] Resinous composition. [g] M.p. 61–62.5°. [h] Mol. wt., calcd. 642, found 639.

SOCONY-VACUUM LABORATORIES
PAULSBORO, NEW JERSEY RECEIVED SEPTEMBER 18, 1950

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(2) Caesar and Sachanen, *Ind. Eng. Chem.*, **40**, 922 (1948).
(3) Greenalgh, U. S. Patent 1,977,627.
(4) Jordan, U. S. Patent 1,854,940.
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(6) McGreal, Niederl and Niederl, THIS JOURNAL, **61**, 345 (1939).
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The Separation of Mixtures of Mono- and Di-substituted Alkyl Phosphoric Acids[1]

BY D. C. STEWART AND H. W. CRANDALL

A number of alkyl phosphoric acids are available commercially, but only as mixtures of the mono- (H_2RPO_4) and di- (HR_2PO_4) substituted forms. It seems probable that for many purposes it would be desirable to use one or the other of these in a separated state, as, for example, in studying the mechanisms involved in the extraction of amino acids by their use.[2] It has been found that this separation may be readily accomplished by taking advantage of the differences in the distribution of the two forms between two immiscible phases, generally water and some organic solvent. In this latter case, the disubstituted acid favors the organic phase, whereas the monosubstituted compound shows more affinity for the aqueous layer. By choosing the appropriate solvent, it is then possible to water wash all of the H_2RPO_4 out of the organic layer by a series of batch extractions, leaving only the HR_2PO_4;

(1) A portion of this work was performed under the auspices of the Atomic Energy Commission.
(2) E. V. McCollum, A. A. Rider and H. Suss, *Proc. Soc. Exp. Biol. Med.*, **72**, 709 (1949).

and, conversely, similarly to solvent-wash all the di- form away from the mono- form, leaving the latter in a water solution. In the case of the octyl phosphoric acids it was found that the substitution of diethylene glycol for the water phase eliminated difficulty with emulsions and gave distribution coefficients of the right order of magnitude to give satisfactory separation of the two forms.

The distribution of the acids was followed by titrating aliquots of the phases potentiometrically with standardized base, using a Beckman Type G glass electrode *p*H meter. It was assumed throughout that no free phosphoric acid was present, so that the difference in titer between the two breaks of the curve could be taken to represent the amount of H_2RPO_4 present, and the difference between this quantity and the titer to the first break to represent the HR_2PO_4. Using this method, the values shown in Table I were obtained for the acid strengths of the commercial mixtures as purchased. The distribution coefficients of the acids between the various pairs of immiscible phases were then similarly obtained, and these are summarized in Table II.

TABLE I

COMPOSITION OF COMMERCIAL ALKYL PHOSPHORIC ACIDS

Phosphoric acid	Source	Concentrations, *M* H_2RPO_4	Concentrations, *M* HR_2PO_4
Ethyl-	Eastman	4.66	4.36
n-Propyl-	Eastman	4.36	3.15
n-Butyl-	Eastman	3.28	2.48
Isobutyl-	Monsanto	3.57	2.56
n-Amyl-	Monsanto	3.48	1.81
n-Octyl-	Monsanto	2.01	1.75

TABLE II

DISTRIBUTION OF ACIDS BETWEEN IMMISCIBLE PHASES

Phosphoric acid	Distribution coefficient (*E*) into solvents from water Solvent	$E_{H_2RPO_4}$	$E_{HR_2PO_4}$
Ethyl-	*n*-Primary amyl alcohol	0.69	1.7
	Dibutyl carbitol	.14	0.51
n-Propyl-	*n*-Primary amyl alcohol	.86	5.4
	Dibutyl carbitol	1.4	1.2
n-Butyl-	*n*-Primary amyl alcohol	2.9	>1000?
	Dibutyl carbitol	2.1	39
	Dibutyl ether	0.66	15
Isobutyl-	Dibutyl ether	.54	11
n-Amyl-	Dibutyl ether	.72	6.2
n-Octyl-	Diethyl ether	42	~760
	Methyl isobutyl ketone	28	~106
n-Octyl-	Dibutyl ether	0.44[a]	7.0[a]

[a] Out of diethylene glycol rather than water.

For batch type washing, the most satisfactory separation is obtained when the HR_2PO_4 distribution coefficient is greater than 5, coupled with a corresponding *E* value of less than 1 for the H_2RPO_4 form. The use of counter-current column extraction techniques, however, should make separations feasible even though the two *E* values differ by a much smaller factor.

Using this technique, completely separated solutions of diethylphosphoric acid in *n*-amyl alcohol, dipropylphosphoric acid in isopropyl and dibutyl ethers, dibutylphosphoric acid in *n*-amyl alcohol and in dibutyl ether, diisobutylphosphoric acid in dibutyl ether, diamylphosphoric acid in dibutyl ether, dioctylphosphoric acid in dibutyl ether and monobutylphosphoric acid in water have all been prepared.

RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA AND
CALIFORNIA RESEARCH AND DEVELOPMENT CO.
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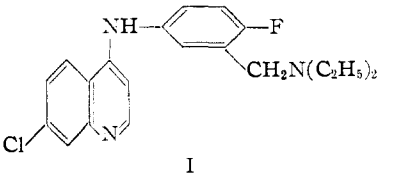
Synthesis of 2-Diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene Dihydrobromide

BY AUGUST SVEINBJORNSSON AND CALVIN A. VANDERWERF

In continuation of our studies on the replacement of amino and hydroxyl groups with the isosteric fluorine atom in medicinal agents of proved value, we have synthesized 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene (I) the fluoro isostere of the antimalarial drug Camoquin



I

[4-(7-chloro-4-quinolylamino)-α-diethyl-amino-*o*-cresol][1] in which the OH-group in Camoquin is replaced by a fluorine atom.

Of the various synthetic routes explored, the best method for the preparation of the desired compound involved the following steps: *o*-toluidine → *o*-fluorotoluene → *o*-fluorobenzoic acid → *o*-fluorobenzyl alcohol → *o*-fluorobenzyl bromide → 2-fluoro-5-nitrobenzyl bromide → 2-diethylaminomethyl-4-nitrofluorobenzene hydrobromide → 2-diethylaminomethyl-4-aminofluorobenzene dihydrobromide → dihydrobromide of I.

The antimalarial activity of I was found to be considerably less than that of Camoquin.

Experimental

Preparation of Known Intermediates.—*o*-Fluorotoluene was prepared in 60% yield by direct diazotization of *o*-toluidine in anhydrous hydrogen fluoride, followed by decomposition of the diazonium fluoride in refluxing hydrogen fluoride. The *o*-fluorotoluene was oxidized to *o*-fluorobenzoic acid in 75% yield by the general method of Clark and Taylor,[2] and the acid was reduced to *o*-fluorobenzyl alcohol in 81% yield by means of a 2.5 molar quantity of lithium aluminum hydride.[3] Treatment of the alcohol with anhydrous hydrogen bromide in benzene gave an 81% yield of the highly lachrymatory *o*-fluorobenzyl bromide.

2-Fluoro-5-nitrobenzyl Bromide.—To 200 ml. of fuming nitric acid (sp. gr. 1.5) at 0°, 25.0 g. (0.13 mole) of *o*-fluorobenzyl bromide was added dropwise with stirring. The mixture was then allowed to come to room temperature with stirring and poured onto ice. The yellow product which precipitated was filtered, washed with cold water, and recrystallized from ethanol to yield 25.0 g. (81%) of pure **2-fluoro-5-nitrobenzyl bromide**, m.p. 76.6–77.4°.

(1) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, THIS JOURNAL, **70**, 1363 (1948).

(2) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 135.

(3) See R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947), for the general method.