[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF KANSAS]

Some Derivatives of Benzoyl and Furoyl Isothiocyanates and their Use in Synthesizing Heterocyclic Compounds[1]

BY IRWIN B. DOUGLASS AND F. B. DAINS

In contrast to the mustard oils, the very reactive acyl isothiocyanates have been little employed in synthesis[2] and hence a further study has been made to determine the effects of their acyl groups.

Benzoyl isothiocyanate readily combines with arylaminoethanols, phenylaminopropanol, phenylaminoacetic acid, or anthranilic acid. Dehydration of the resulting thioureas yields thiazolidines, a thiazane, a 2-thioimidazolone, or a quinazoline derivative as the case may be. Desulfurization of the acylethanolthioureas results in forming oxazolidines.

Some thirty acyl isothiocyanates are described in the literature but none is derived from a heterocyclic acid. Accordingly, furoyl isothiocyanate and some derivatives analogous to the known products from benzoyl isothiocyanate have been studied.

Experimental

I. Derivatives of Benzoyl Isothiocyanate

Preparation of Benzoyl Isothiocyanate and Thioureas.—The following procedure resulted, in most cases, in a 70–80% yield of the thioureas.

To 0.1+ mole of NH_4SCN in 25 cc. of hot acetone 0.1 mole of benzoyl chloride was added dropwise. After the initial reaction had subsided, the mixture was heated for five minutes and then a hot solution of amine (0.1 mole) in acetone (25 cc.) was added, slowly and with constant stirring. Upon pouring the mixture into five times its volume of water, the thiourea precipitated either as a solid or a slowly crystallizing oil. The product was purified by crystallizing from alcohol. Anhydrous reagents were found to be necessary to ensure satisfactory yields.

Ethanolthioureas and Thiazolidines.—β-Benzoyl-α-ethanol-α-phenylthiourea, I, prepared from benzoyl mustard oil and phenylaminoethanol, upon standing for forty-eight hours in 80% sulfuric acid or in 48% hydrobromic acid[3] condensed to 2-benzoylimino-3-phenylthiazolidine, II, in 80–90% yield. The constitution of this thiazolidine follows from its hydrolysis to 2-keto-3-phenylthiazolidine.[4]

Unsuccessful attempts were made to prepare 2-imino-3-phenylthiazolidine from the benzoyl derivative. Careful heating with the molar quantity of alcoholic sodium hydroxide gave a product (m. p. 173–174°) of undetermined structure.

The thioureas formed from benzoyl isothiocyanate and *o*- and *p*-tolylaminoethanols, IV, and VII, and aminoethanol, X, formed similar benzoyliminothiazolidines, V, VIII, and XI.

When the ethanolthioureas I, IV, and VII were treated with yellow mercuric oxide in benzene[3,5] oxazolidines III, VI, and IX resulted.

Thiazane Derivative.—α-Phenylaminopropanol and benzoyl isothiocyanate yielded β-benzoyl-α-phenyl-α-propanolthiourea, XII, which was condensed to 2-benzoylimino-3-phenylthiazane, XIII, by the action of sulfuric acid.

Derivatives of Ethyl Phenylamino-acetate.—The benzoylthiourea, XIV, upon treatment with sulfuric acid lost a mole of ethyl alcohol and became 3-benzoyl-1-phenyl-2-thioimidazolone, XV.[6]

β-Benzoyl-α-phenylthioureidoacetic acid, XVI, was prepared by the action of benzoyl isothiocyanate on phenylaminoacetic acid and also by the hydrolysis of the ester, XIV, with sodium hydroxide. Sulfuric acid condensed it to the imidazolone, XV.

Reactions with Anthranilic Acid.—The benzoylthiourea, XVII, melted at 159–160° with decomposition, resolidified, and then melted at 190–200°. A quantity, heated for twenty minutes at 160–175°, evolved hydrogen sulfide, and formed an unidentified sulfur-free product (N, 10.52; m. p. 207–208°).

The thiourea, XVII, on treatment with sulfuric acid, formed 3 - benzoyl - 4 - keto - 2 - thiotetrahydroquinazoline, XVIII, melting at 157–158°. On hydrolysis with sodium hydroxide, benzoic acid and 4-keto-2-thiotetrahydroquinazoline, XIX (m. p. 305–310°),[7] were obtained.

Hydrolysis of XVII with sodium hydroxide gave the same quinazoline, XIX, and not the expected thioureido benzoic acid.

Thioether of XIX.—Careful methylation of XIX, using the minimum amount of sodium hydroxide to ensure solution and an equivalent amount of methyl sulfate gave the methyl thioether, XV, which was soluble in alcohol and in sodium hydroxide. When fused with aniline XV gave 2-anilino-4-ketodihydroquinazoline.[8]

3-Methyl-2,4-diketotetrahydroquinazoline (m. p. 236°), XXI,[9] along with a strong odor of mercaptan resulted when the benzoylenethiourea, XIX, was treated in alkaline solution with an excess of methyl sulfate.

(1) Taken from a thesis presented by Irwin B. Douglass in partial fulfilment of the requirements for the Ph.D. degree.

(2) *Cf.* Dixon, *J. Chem. Soc.*, **71**, 617–641 (1897); **75**, 403 (1899); Dixon and Taylor, *ibid.*, **101**, 558 (1912); **109**, 1261 (1916); Johnson, *Am. Chem. J.*, **30**, 178 (1903); Wheeler and Dustin, *ibid.*, **24**, 428 (1900); Wheeler and Sanders, THIS JOURNAL, **22**, 377 (1900).

(3) Dains, Brewster and others, *ibid.*, **44**, 2639 (1922); **47**, 1983 (1925).

(4) Will, *Ber.*, **15**, 344 (1882).

(5) Dains and others, Univ. of Kansas Sci. *Bull.*, **20**, 161–167 (1931).

(6) *Cf.* Dains and others, THIS JOURNAL, **44**, 2313 (1922).

(7) *Cf.* Dyson and George, *J. Chem. Soc.*, **125**, 1708 (1924); Rupe, *Ber.*, **30**, 1098 (1898); Stewart, *J. prakt. Chem.*, [II] **44**, 416 (1891).

(8) Deck and Dains, THIS JOURNAL, **55**, 4988 (1933); Johnson and others, *ibid.*, **25**, 797–798 (1903).

(9) Abt, *J. prakt. Chem.*, [II] **39**, 147 (1889); Bogert and Scatchard, THIS JOURNAL, **41**, 2062 (1919).

TABLE I

DERIVATIVES OF BENZOYL ISOTHIOCYANATE

No.	Compound	Formula	M. p., °C.	Analyses, % N Calcd.	Found
I	β-Benzoyl-α-ethanol-α-phenylthiourea	$C_{16}H_{16}N_2O_2S$	154	9.33	9.38
II	2-Benzoylimino-3-phenylthiazolidine	$C_{16}H_{14}N_2OS$	122	9.93	10.07
III	2-Benzoylimino-3-phenyloxazolidine	$C_{16}H_{14}N_2O_2$	117	10.53	10.42
IV	β-Benzoyl-α-ethanol-α-(*o*-tolyl)-thiourea	$C_{17}H_{18}N_2O_2S$	141	8.92	8.92
V	2-Benzoylimino-3-(*o*-tolyl)-thiazolidine	$C_{17}H_{16}N_2OS$	137–138	9.46	9.58
VI	2-Benzoylimino-3-(*o*-tolyl)-oxazolidine	$C_{17}H_{16}N_2O_2$	103	10.00	9.91
VII	β-Benzoyl-α-ethanol-α-(*p*-tolyl)-thiourea	$C_{17}H_{18}N_2O_2S$	136	8.92	8.97
VIII	2-Benzoylimino-3-(*p*-tolyl)-thiazolidine	$C_{17}H_{16}N_2OS$	154	9.46	9.45
IX	2-Benzoylimino-3-(*p*-tolyl)-oxazolidine	$C_{17}H_{16}N_2O_2$	134	10.00	9.96
X	β-Benzoyl-α-ethanolthiourea	$C_{10}H_{12}N_2O_2S$	128	12.50	12.61
XI	2-Benzoyliminothiazolidine	$C_{10}H_{10}N_2OS$	168	13.59	13.54
XII	β-Benzoyl-α-phenyl-α-propanolthiourea	$C_{17}H_{18}N_2O_2S$	94	8.92	8.68
XIII	2-Benzoylimino-3-phenylthiazane	$C_{17}H_{16}N_2OS$	137	9.46	9.41
XIV	Ethyl (β-Benzoyl-α-phenylthioureido)-acetate	$C_{18}H_{18}N_2O_3S$	165	8.19	7.98
XV	3-Benzoyl-1-phenyl-2-thio-4-imidazolone	$C_{16}H_{12}N_2O_2S$	163	9.46	9.67
XVI	(β-Benzoyl-α-phenylthioureido)-acetic acid	$C_{16}H_{14}N_2O_3S$	166–167	8.92	9.01
XVII	*o*-(β-Benzoylthioureido)-benzoic acid	$C_{15}H_{12}N_2O_3S$	160	9.21	9.41
XVIII	3-Benzoyl-4-keto-2-thiotetrahydroquinazoline	$C_{15}H_{10}N_2O_2S$	158	9.76	9.78
XIX	4-Keto-2-thiotetrahydroquinazoline	$C_8H_6N_2OS$	305–310	15.73	15.88
XX	4-Keto-2-methylthiodihydroquinazoline	$C_9H_8N_2OS$	219	14.59	14.63
XXI	2,4-Diketo-3-methyltetrahydroquinazoline	$C_9H_8N_2O_2$	236	15.84	15.93
XXII	?-Methylthio-1,?-diphenyl-?-thiodihydrotriazine	$C_{16}H_{13}N_3S_2$	211	13.50	13.48

Triazine Formation.—The methyl ether of phenylthiourea with benzoyl isothiocyanate gave a poor yield of a yellow compound, XXII, which is probably a triazine[10] of the structure: A $C_6H_5NC(SCH_3)NCSNC(C_6H_5)$ or B $C_6H_5NC(SCH_3)NC(C_6H_5)NCS$.

II. Derivatives of Furoyl Isothiocyanate

Furoyl chloride was prepared in 80% yield by allowing 112 g. of finely ground furoic acid (technical) and 250 g. of thionyl chloride to react at 80–90° until gas evolution had practically ceased (one to two hours). The furoyl chloride was then separated from unchanged thionyl chloride by fractional distillation.

Furoyl isothiocyanate was not isolated but was used in acetone solution with the amines to form thioureas. The yields with aryl amines were 70–80% but those with aliphatic amines were lower.

Hydrolysis.—The furoyl group was removed from a number of the disubstituted thioureas, XXIV–XXX, by boiling for five minutes with 10% sodium hydroxide, leaving monosubstituted thioureas which were readily identified. α-Benzyl-β-furoyl-α-phenylthiourea, XXXIV, was more difficult to hydrolyze than the disubstituted compounds.[11] Hydrolysis was accomplished by refluxing for eight hours 15 g. of the thiourea with 3 g. of sodium hydroxide in 100 cc. of alcohol. Recrystallization of the

TABLE II

DERIVATIVES OF FUROYL ISOTHIOCYANATE

No.	Compound, thiourea	Formula	M. p., °C.	Analyses, % N Calcd.	Found
XXIII	Furoyl-	$C_6H_6N_2O_2S$	183	16.47	16.63
XXIV	α-Furoyl-β-methyl-	$C_7H_8N_2O_2S$	142	15.22	15.31
XXV	α-Furoyl-β-ethyl-	$C_8H_{10}N_2O_2S$	101–102	14.14	14.32
XXVI	α-Benzyl-β-furoyl-	$C_{13}H_{12}N_2O_2S$	122	10.77	10.78
XXVII	α-Furoyl-β-phenyl-	$C_{12}H_{10}N_2O_2S$	116	11.38	11.34
XXVIII	α-Furoyl-β-(*o*-tolyl)-	$C_{13}H_{12}N_2O_2S$	115–116	10.77	10.59
XXIX	α-Furoyl-β-(*m*-tolyl)-	$C_{13}H_{12}N_2O_2S$	99	10.77	10.82
XXX	α-Furoyl-β-(*p*-tolyl)-	$C_{13}H_{12}N_2O_2S$	130	10.77	10.72
XXXI	α-Furoyl-β-(α-naphthyl)-	$C_{16}H_{12}N_2O_2S$	186	9.46	9.29
XXXII	α-Furoyl-β-(β-naphthyl)-	$C_{16}H_{12}N_2O_2S$	139–140	9.46	9.45
XXXIII	β-Furoyl-α-methyl-α-phenyl-	$C_{13}H_{12}N_2O_2S$	98–99	10.77	10.71
XXXIV	α-Benzyl-β-furoyl-α-phenyl-	$C_{19}H_{16}N_2O_2S$	124	8.33	8.31
XXXV	β-Furoyl-α,α-diphenyl-	$C_{18}H_{14}N_2O_2S$	139–140	8.70	8.71
XXXVI	α-Ethanol-β-furoyl-α-phenyl-	$C_{14}H_{14}N_2O_3S$	111	9.65	9.62
XXXVII	2-Furoylimino-3-phenylthiazolidine	$C_{14}H_{12}N_2O_2S$	123	10.30	10.44

(10) *Cf.* Johnson, *Am. Chem. J.*, **30**, 178 (1903).

(11) *Cf.* Dixon, *J. Chem. Soc.*, **67**, 1044 (1895); **85**, 811 (1904); Dixon and Taylor, *ibid.*, **93**, 690 (1908).

solidified oil left after steam distilling the mixture gave a 50% yield of α-benzyl-α-phenyl-thiourea (m. p. 138–139°). In a similar manner β-furoyl-α,α-diphenylthiourea, XXXV, yielded unsymmetrical diphenylthiourea (m. p. 217°).

Thiazolidine Formation.—With phenylaminoethanol, furoyl isothiocyanate yielded α-ethanol-β-furoyl-α-phenylthiourea, XXXVI. Treatment with 80% sulfuric acid gave 2-furoylimino-3-phenylthiazolidine, XXXVII. Alkaline hydrolysis of this product formed the same 173–174° melting compound obtained from II.

Summary

Benzoyl isothiocyanate has been utilized in synthesizing a number of new heterocyclic compounds.

Furoyl isothiocyanate has been prepared and a number of its derivatives have been described. Methods of hydrolyzing some of these compounds have been given.

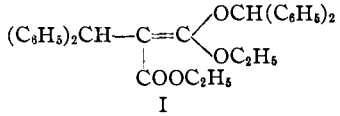
LAWRENCE, KANSAS RECEIVED DECEMBER 8, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

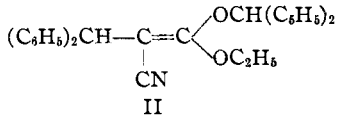
The Structure of Ethyl Di-diphenylmethylmalonate

BY ARTHUR C. COPE[1]

While several O-alkyl and acyl derivatives of the enolic form of ketones and ketonic esters are known, very few O-alkyl derivatives of ester enols (ketene acetals) are recorded. Of the latter class of compounds only two have been obtained by direct alkylation of ester enolates. They are ethyl O-diphenylmethyl diphenylmethylmalonate (I)[2] and the corresponding derivative of ethyl cyanoacetate (II).[3] A study of

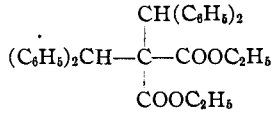


I



II

I was undertaken in order to determine if it could be transformed into the corresponding dialkyl malonic ester (III) by a rearrangement

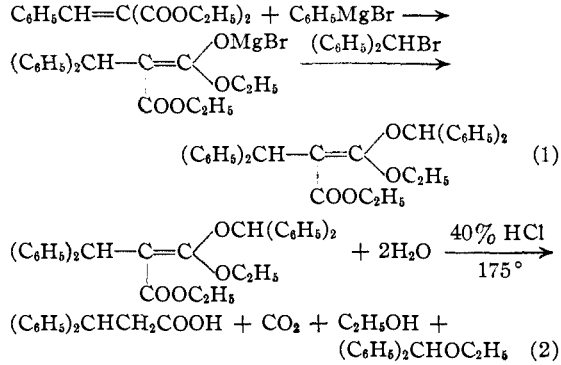


III

involving migration of the diphenylmethyl group from oxygen to carbon.

Before attempting the rearrangement of I into III it seemed advisable to prepare III by the ordinary malonic ester synthesis and determine its properties. However, the product obtained by alkylating the sodium derivative of ethyl diphenylmethylmalonate with diphenylmethyl bromide proved to be identical with the compound originally prepared by Kohler and regarded as a ketene acetal (I). This observation must lead to one of two conclusions: either the ketene acetal structure (I) is incorrect and the compound is really ethyl di-diphenylmethylmalonate (III), or the malonic ester synthesis in this case has given an O-alkyl derivative.[4]

The structure I was based on the method of synthesis and the products of hydrolysis.



(1)

(2)

The method of synthesis is now known to be inconclusive as evidence for structure I, since other bromo-magnesium enolates have been observed to yield C-acyl derivatives.[5,6] However, in order to explain the products of hydrolysis on the basis of formula III, the cleavage of a

(1) National Research Fellow in Chemistry. The author wishes to express his indebtedness to Professor E. P. Kohler for advice and criticism.

(2) Kohler, *Am. Chem. J.*, **34**, 132 (1905).

(3) Kohler and Reimer, *ibid.*, **33**, 348 (1905).

(4) While no cases are recorded in which alkylation of sodium enol malonic esters yielded O-alkyl derivatives, branched chain dialkyl malonic esters have been studied but little because of the difficulty encountered in introducing the second alkyl group. Because of this fact and since the products of hydrolysis of the compound are more easily explained on the basis of formula I, it seemed unwise to interpret the method of synthesis as evidence for formula III.

(5) Kohler and Peterson, THIS JOURNAL, **55**, 1073 (1933).

(6) Kohler and Tishler, *ibid.*, **54**, 1596 (1932).