Heterocyclic Compounds. VI. Synthesis of Polynuclear Thienopyrimidine Derivatives (1)

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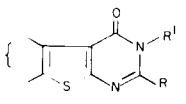
Received January 19, 1976

Quinazoline derivatives have received great interest because of their potential biological activity. This communication describes a facile method for the synthesis of substituted thiophenopyrimidones. 2-Amino-3-carbethoxy-4,5-tetramethylenethiophene on heating with substituted imidoylchlorides, iminoethers, iminothioethers or thioamides affords thiophenopyrimidones. By using this method a number of such compounds of varying complexity were synthesized which are otherwise not so easily accessible.

J. Heterocyclic Chem., 13, 903 (1976).

In an earlier communication (2), we described the synthesis of several substituted thienopyrimidines of the general structure (**1**). Several additional reports have appeared in the literature which describe the synthesis and biological activity (3-5) of these types of compounds. We have found that the formation of such compounds *via* the azlactone method (2) is not a very clean reaction and yields are unsatisfactory. In the present communication we describe a facile method which not only can be employed for generating these compounds but can also be conveniently extended to the synthesis of more complex policyclic heterocycles.

Iminoethers (6-8) and iminochlorides (9,10) are known to react with *o*-aminoesters to yield quinazolones. We have found that this reaction can also be used for the synthesis of thienopyrimidones. Thus, when 2-amino-3-carboethoxy-4,5-tetramethylenethiophene (**2**) (11) was heated with *N*-arylbenzimidoyl chloride (10) (**3a**) for about half an hour and a methylene chloride solution of the melt passed over a Florisil column, 2,3-diphenyl-4-oxo-5,6-tetramethylenethieno[2,3-*d*]pyrimidine (**4a**) was obtained in 70% yield. By using the same general procedure and an appropriate iminochlorides the thienopyrimidones **4b**, **4c**, and **4d** were also obtained.



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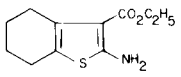

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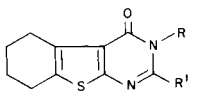

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a. R = R^1 = Ph
b. R = Ph, R^1 = *p*-$CH_3C_6H_4$
c. R = CH_2CH_2Ph, R^1 = Ph
d. R = *m*-$CH_3C_6H_4$, R^1 = *t*-Bu
e. R = Ph, R^1 = CH_3

This reaction of the iminochlorides was then extended to 2-chloropyridine which also has the N=C-Cl moiety. It was found that the fusion of 2-chloropyridine with **2** resulted in the tetracyclic compound **7** (80% yield) under similar conditions. The iminochloride moiety in such diverse structural environments as in 2-chlorothiazole, 2-chlorobenzothiazole, 4-chloro-5,6-tetramethylenethieno-[2,3-*d*]pyrimidine (**5**) (12), and 6-chloro-2-methyl-7,8,9, 10-tetrahydrophenanthridine (13) (**6**) was also found to be reactive enough to provide cyclization reactions with **2**. The polycyclic derivatives **8**, **9**, **10**, and **11** obtained from the above mentioned chlorocompounds in a simple, one step process and in good yield are not otherwise easily accessible. However, when 2-chloro-3-methylquinoxaline was similarly treated with **2** no cyclization reaction was observed. The sole product of this reaction under a variety of experimental conditions was the *N*-alkylated product

Table I

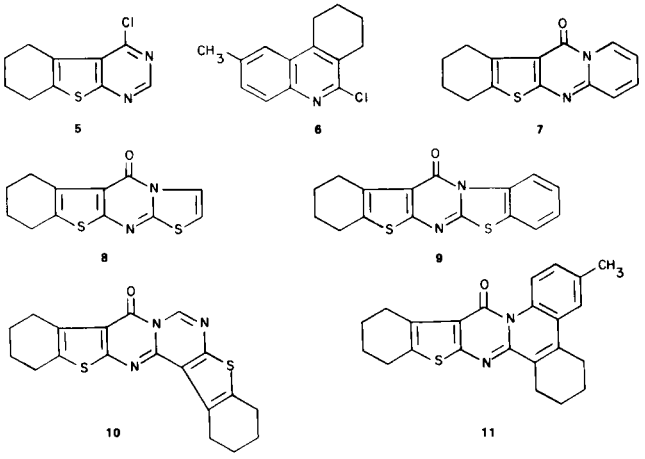
Analytical and Spectral Data

Compound No.	M.p. °C	Yield	Formula	Analysis C	H	N	Spectral Data
4a	146-148	70	$C_{22}H_{18}N_2OS$	74.11 (73.73)	5.38 (5.06)	7.47 (7.82)	Ir: 1660 cm^{-1}; nmr δ: 1.8-2.0 (b, 4H), 2.8-3.1 (b, 4H), 7.15 (s, 5H), 7.25 (s, 5H); M^+ at m/e 358.
4b	171-173	60	$C_{23}H_{20}N_2OS$	74.07 (74.17)	5.41 (5.41)	7.33 (7.52)	Ir: 1670 cm^{-1}; nmr δ: 1.7-1.9 (b, 4H), 2.5-2.8 (b, 4H), 3.95 (s, 3H), 6.8 (s, 5H), 7.6-7.8 (b, 4H); M^+ at m/e 372.
4c	140-142	68	$C_{24}H_{22}N_2OS$	74.73 (74.59)	5.75 (5.74)	7.25 (7.25)	Ir: 1660 cm^{-1}; nmr δ: 1.9 (b, 4H), 2.9 (m, 6H), 4.25 (m, 2H), 6.95-7.6 (m, 10H); M^+ at m/e 386.
4d	233-234	75	$C_{21}H_{24}N_2OS$	71.90 (71.57)	7.02 (6.86)	7.75 (7.95)	Ir: 1655 cm^{-1}; nmr δ: 1.2 (s, 9H), 1.8-2.0 (b, 9H), 2.35 (s, 3H), 2.3-3.0 (b, 4H), 7.1-7.3 (m, 4H), M^+ at m/e 352.
4e (2)	132-133	72	$C_{17}H_{16}N_2OS$				
7	201-202	80	$C_{14}H_{12}N_2OS$	65.62 (65.50)	4.72 (5.00)	10.93 (10.58)	Ir: 1675 cm^{-1}; nmr δ: 1.7-2.0 (b, 4H), 1.6-3.2 (b, 4H), 6.8-7.1 (m, 1H), 7.45-7.55 (m, 2H), 8.9-9.1 (m, 1H); M^+ at m/e 256.
8	234-235	65	$C_{12}H_{10}N_2OS_2$	54.99 (54.97)	3.86 (3.84)	10.56 (10.68)	Ir: 1670 cm^{-1}; M^+ at m/e 262.
9	204-205	70	$C_{16}H_{12}N_2OS_2$	61.40 (61.54)	3.95 (3.87)	8.91 (8.97)	Ir: 1680 cm^{-1}; nmr δ: 1.8-2.0 (b, 4H), 2.7-3.1 (b, 4H), 7.4-7.7 (m, 3H), 8.9-9.2 (m, 1H); M^+ at m/e 312.
10	205-207	65	$C_{19}H_{17}N_3OS_2$	62.00 (62.12)	4.54 (4.66)	11.72 (11.44)	Ir: 1675 cm^{-1}; M^+ at m/e 367.
11	234-235	60	$C_{23}H_{22}N_2OS$	73.70 (73.78)	6.12 (5.92)	7.51 (7.48)	Ir: 1680 cm^{-1}; nmr δ: 1.8-2.1 (b, 8H), 2.8-3.0 (b, 8H), 2.4 (s, 3H), 7.1-7.35 (b, 3H); M^+ at m/e 374.
12a	154-156	65	$C_{20}H_{21}N_3O_2S$	65.70 (65.38)	5.82 (5.76)	11.50 (11.44)	Ir: 1640 cm^{-1}; nmr δ: 1.5 (t, 3H, J = 8 Hz), 1.7-1.9 (b, 4H), 2.6-2.8 (b, 4H), 2.75 (s, 3H), 4.35 (q, 2H, J = 8 Hz), 7.3-8.0 (m, 4H), M^+ at m/e 367.
12b	143-144	75	$C_{25}H_{26}N_2O_3S$	68.90 (69.11)	5.84 (6.03)	6.52 (6.45)	Ir: 1640 cm^{-1}: 1.35 (t, 3H, J = 7 Hz), 1.85-2.0 (b, 4H), 2.8-3.1 (b, 4H), 3.52 (s, 3H), 4.35 (b, 2H), J = 7 Hz), 6.8 (b, 4H), 7.3 (s, 5H); M^+ at m/e 434.
15	209-210	75	$C_{13}H_{14}N_2OS_2$	56.17 (56.11)	5.03 (5.07)	10.07 (10.07)	Ir: 1680 cm^{-1}; nmr δ: 1.15-1.45 (m, 4H), 1.8-2.5 (b, 4H), 2.8-3.0 (b, 4H), 3.4-3.6 (b, 2H); M^+ at m/e 278.
16	150-151	80	$C_{15}H_{18}N_2OS$	65.68 (65.62)	6.61 (6.59)	10.21 (10.21)	Ir: 1685 cm^{-1}; nmr δ: 1.8-2.0 (b, 10H), 2.6-3.2 (b, 6H), 4.2-4.4 (b, 2H); M^+ at m/e 274.

(**12a**). In a similar reaction, **2** failed to provide the cyclic pyrimidine derivative with *N*-(*o*-anisyl)benzimidoyl chloride (**3**, R = *o*-$Ch_3OC_6H_4$, R^1 = Ph) and instead the *N*-alkylated product **12b** was isolated.

The reaction of **3** with anthranilic acid was interesting. Chromatographic separation of the products indicated the presence of the unreacted anthranilic acid, 2,3-diphenyl-4-quinazolone (10) and benzanilide. The quinazolone and benzanilide were present roughly in equimolar proportions in the reaction product even when the reaction was carried out under anhydrous conditions. It appears that during this reaction the water produced in the cyclization step hydrolyzes the iminochloride to the benzanilide (10).

The reaction of thioimidates with **2** was also investigated. Heating **2** with **13a** (14) resulted in the isolation of **4a** which was identical in all respects with the product obtained by treating **2** with **3a**. Similarly, the reaction of **13b** with **2** gave **4e** (2). The thioimidates **13a** also reacted



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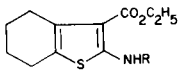
8 9

10 11



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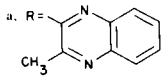
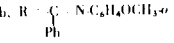


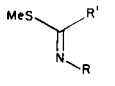
a, R =



b, R =

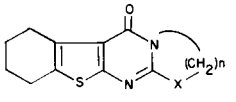
with anthranilic acid under the same reaction conditions to give 2,3-diphenyl-4-quinazolone in 60% yield (10). We have found that the yields of thienopyrimidones obtained by treating amino esters with thioimidates or imidoyl chlorides are comparable.

Because of the greater enolizability of thioamides as compared to the corresponding amides we were interested in exploring their reaction with amino esters to form the pyrimidine ring. No reaction was observed when **2** was treated with thiobenzanilide and the reactants were recovered unchanged. The 5-membered cyclic thioamides in various structural environments, such as, 2-mercapto thiazoline, 2-imidazolidinethione and 3-*N*-ethyl-5-benzyl-2-thiohydantoin (15) also failed to react with the amino-ester **2** to form the pyrimidine derivatives. When the 6-membered thioamide, 3,4,5,6-tetrahydro-2-pyrimidine thiol, was heated with **2** the tetracyclic product **14** was obtained in very poor yield. The formation of **14** was confirmed only through the mass spectral analysis of the product which showed a molecular ion peak at m/e 261 ($C_{13}H_{15}N_3OS$). Interestingly enough the reaction of 2-mercapto-5,6-dihydro-4*H*-3-thiazine (16) with **2** resulted in the formation of **15** in 85% yield (17). The reaction of a seven-membered thiolactam, ω-thiocaprolactam, was also investigated. It was found that its reaction with **2** gave **16** in about 10% yield. The identity of **16** was confirmed by its comparison with the product derived from the reaction of **2** with 1-aza-2-methoxy-1-cycloheptene (18).



13

a, R = R^1 = Ph
b, R = Ph, R^1 = CH_3



14, X = NH, n = 3
15, X = S, n = 3
16, X = CH_2, n = 4

Acknowledgment.

We wish to thank Stevens Institute of Technology for the support of this work and Miss S. Shah and Mr. M. Anter for technical assistance.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer Infracord. Nmr spectra were recorded with a Varian A60A spectrometer using deuterated chloroform or dimethylsulfoxide-d_6 and mass spectra with a 21-103C CEC spectrometer. Microanalyses were performed by MHW Laboratories, Garden City, Michigan, and A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mulheim (Ruhr), West Germany.

General Procedure for the Reaction Between the *o*-Aminoesters and Imino Derivatives.

A. Imidoyl Chlorides and *o*-Aminoester.

An equimolar mixture of benzimidoyl chloride and 2-amino-3-carboethoxy-4,5-tetramethylenethiophene (**2**) (11) was heated in an oil bath at 175-200° for 4 hours, or heated on a low flame for 15 minutes. On cooling a jelly-like mass was formed. It was chromatographed over florosil using methylene chloride as eluant crystallization from methylene chloride-hexane gave **4a**, m.p. 146° (60%). Using these reaction conditions, the quinazolones **4** and **7-11** were prepared from the appropriate imidoylchlorides and the amino ester **2**.

B. Thioamides and *o*-Aminoester.

In a similar manner **14, 15,** and **16** were obtained by heating **2** with 3,4,5,6-tetrahydro-2-pyrimidinethiol (18), 2-mercapto-5,6-dihydro-4*H*-3-thiazine (16) and ω-thiocaprolactam respectively.

C. Thioimidate and *o*-Aminoester.

The thioimidates **13a** (14) and **13b** on heating with **2** afforded the substituted quinazolones **4a** and **4e** respectively in 70% yield.

D. Iminoether and *o*-Aminoester.

The quinazolone (**16**) was obtained in 80% yield on heating **2** with 1-aza-2-methoxy-1-cycloheptane (18) as described above. The product was recrystallized from methylene chloride-hexane as a colorless powder.

The analytical and spectral data on the quinazolones and other products isolated in the above reactions are given in Table I.

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(18) This compound was obtained from Aldrich Chemical Company, Inc., Milwaukee, Wis. 53233.