Synthesis of some new tetracyclic heteroaromatic chromans via quinone methide intermediates

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Synthesis of several new tetracyclic heteroaromatic chromans has been achieved through the reaction of various uracil and 1,3-thiazine derivatives with 1,2-naphthoquinone-1-methide. The spirodimer **4** is a better source of naphthoquinone methide than the naphthol derivatives which provide chromans in low yield due to side reactions. The structure and mechanisms of the various products formed are discussed.

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On a réalisé la synthèse de plusieurs chromanes tétracycliques hétéroaromatiques en faisant appel à la réaction de divers dérivés de l'uracile ou de la thiazine-1,3 avec le méthide-1 de la naphtoquinone-1,2. Le spiro-dimère **4** est une meilleure source de méthide-1 de la naphtoquinone-1,2 que les dérivés du naphtol qui ne fournissent les chromanes qu'avec de faibles rendements par suite des réactions secondaires. On discute de la structure et du mécanisme de formation des divers produits.

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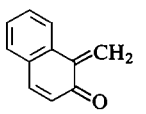
Introduction

As a suitable model approach to the preparation of some potentially biologically active chroman derivatives, especially those fused to other heterocyclic nuclei, we have examined the reactions of 1,2-naphthoquinone-1-methide, (**1**), with uracil and 1,3-thiazine derivatives. In addition these reactions permit a suitable variation of the nature of groups attached to the 5–6 carbon to carbon bond in the uracil and 1,3-thiazine derivatives respectively, which is expected to be one substrate for the quinone methide in these reactions. However, in such studies it is known (1) that the *o*-quinone methide may react in either a dipolar form, **2**, or a diradical form, **3**. Thus although **1** may add stereo- and regiospecifically to *cis* or *trans* stilbene via a (4 + 2) cycloaddition (2*a*), the reaction of **1** with ethyl maleate or fumarate proceeds nonstereospecifically and thus gives the same products (2*a*, *b*). Also its addition to dihydropyran, vinyl ethers, and unsaturated esters occurs via a polar mechanism, while the formation of the *o*-quinone methide spiro dimer, **4**, and a benzofuran adduct indicates a diradical mechanism. The reactivity has been rationalized in terms of ready polarizability of *o*-quinone methide by the substrate (2*c*).



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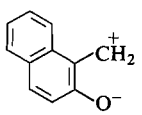

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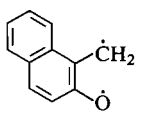

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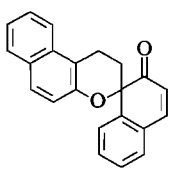

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Results

In these studies, *o*-quinone methides were made by *in situ* thermal decomposition of the spirodimer (**4**) in refluxing mesitylene, which provides a better source than other methods, such as thermal elimination of water, methanol, or dimethylamine from 2-naphthol derivatives (2*b*). These methods are unsuitable because of side reactions, especially those induced by the above eliminated species (3–11). Some of the various uracil (**5***a–d*) and 1,3-thiazine-2-thione derivatives (**6**) were prepared by literature methods (12–15) or were commercially available. The preparation of one other (**5***e*) is described.

The reaction with 1,3-dimethyluracil (**5***a*) gave two products. One of these appears to be a chroman, assigned the structure **7***a*. This compound is likely formed by a (4 + 2) cycloaddition reaction. A *cis* geometry is indicated since the coupling constant of the protons on the bridgehead carbon atoms ($J_{2,3}$) is 2.5 Hz. This value is too small to indicate a *trans* fused ring system. It is known that dihydropyran, coumarin, 1,4-napthoquinone, and other unsaturated substrates also give adducts with *cis* geometry with *o*-quinone methides (2*a*), and with similar *J* values. The other product appears to be a phenol, assigned the structure **8***a*, indicated by an ir absorption at 3300 cm^{-1} and a peak in the nmr spectrum at δ 6.68, assigned to the olefinic proton

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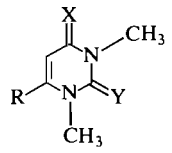
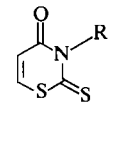


5

a X = Y = O, R = H
b X = S, Y = O, R = H
c X = Y = S, R = H
d X = Y = O, R = CH_3
e X = S, Y = O, R = CH_3



6

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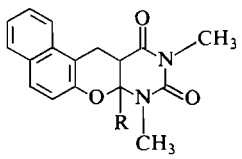
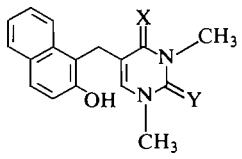
b R = CH_3



7

a R = H
b R = CH_3



8

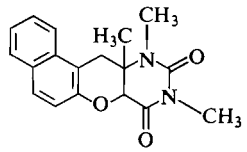
a X = Y = O
b X = S, Y = O
c X = Y = S

on the uracil nucleus. The peak appears to be slightly broadened, possibly by *cis* allylic coupling to the two methylene protons. This phenol probably arises from the fission of the chroman ring in **7***a* by a mechanism similar to that proposed for an *o*-quinone methide – indole adduct (2*b*), involving electron release from the nitrogen atom. The adduct **7***a* was not converted to **8***a* by chromatography on silica gel, a possible acidic catalyst, indicating that it is not an artifact of the work-up procedure. This mechanism also seems more likely in view of the results obtained with other uracils, which will be discussed later.

The possible formation of phenol **7***a* from the thermal rearrangement of chroman **8***a* was also investigated by heating pure chroman **8***a* in refluxing mesitylene. No phenol was observed and a careful chromatographic analysis of the reaction mixture gave a small amount of the starting spirodimer, 1,3-dimethyluracil, and 1,1-ethylenedi-2-naphthol, along with resinous material and some unidentified products. Similar retro additions have been reported (2*a*).

1,3-Dimethyl-4-thiouracil (**5***b*) and 1,3-dimethyl-2,4-dithiouracil (**5***c*) gave only the phenols **8***b* and **8***c* respectively. No chroman products were isolated. These structures were confirmed by ir and nmr data. It may be that ring opening of the chroman ring, with regeneration of the conjugated uracil structure, is more favored by the presence of thione sulfur in the uracil ring.

In contrast, the reaction of 1,3,6-trimethyluracil (**5***d*) gave two isomeric chromans. One of these exhibited a multiplet at δ 2.85 to 3.68, consistent with the protons at positions 3 and 4 of the chroman ring in **7***b*. The other compound exhibited two singlets at δ 3.20 and 4.13 assigned to the methylene and methine protons of the isomeric structure **9**, the chroman C-4 and C-2 positions, respectively. No ir absorptions characteristic of phenols were evident. Interestingly, when *o*-quinone methide was treated with 1,3,6-trimethyl-4-thiouracil (**5***e*), it produced, in high yield, an entirely different product. This was a very insoluble material whose analysis showed a loss of a sulfur and a nitrogen atom. Its insolubility has prevented much further investigation of its structure. The reactions of the two 1,3-thiazine-2-thiones (**6***a*, *b*) with the *o*-quinone methide gave in each case a 1:1 cyclic adduct, assigned the structures **10***a*, *b* respectively, and the 2-methyl derivative **11** afforded the adduct **12**. No phenolic products were detected in these reactions. If the fission of the chroman ring occurs by electron release from a heteroatom, N or S in the uracil and thiazine rings respectively, then these results are consistent with the electron releasing effects of these atoms. The formation of π bonds, as would be required by the mechanism of fission, would be less favored for sulfur than nitrogen.



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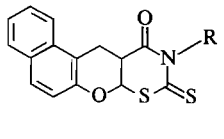
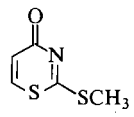


10

a R = H
b R = CH_3



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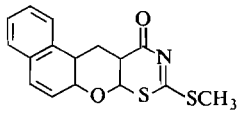

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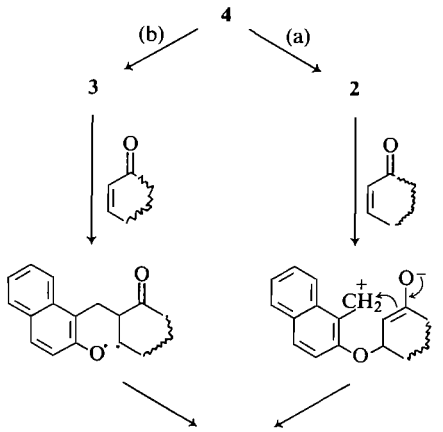
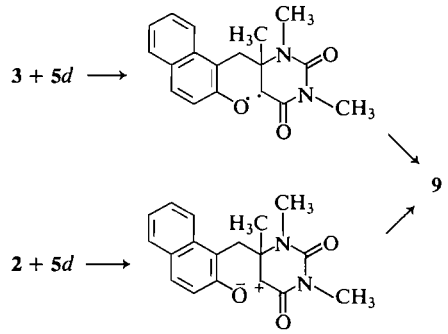
Discussion

In view of the similarity of the double bond substrate in the uracils and thiazines to those in unsaturated esters (2*b*), we favor the ionic mechanism (Scheme 1a) for the formation of all of the above products, except the product **9** (Schemes 1b, 2). Nevertheless a discrete dipolar initial addition product (Scheme 1a) could conceivably cyclize in a *cis* or *trans* fashion. Fortunately, examination of a molecular model and application of ring closure rules (6-*endo* trig, when appropriate resonance structures are considered), also indicates that the *cis* fusion is favored. The formation of product **9** appears to be consistent with a radical mechanism. An ionic mechanism in this case would involve an intermediate which would possess a carbonium ion



7*a*, *b*, 8*a*–*c*, 10*a*, *b*, 12

SCHEME 1



SCHEME 2

adjacent to a carbonyl group. This mechanism could be in agreement with that proposed for benzofuran reactions (2*a*).

The formation of this chroman **9** by a different mechanism only in the case of reaction of **5***d* suggests that the methyl substituent at position 6 has some special bearing on the course of the reaction. It possibly may provide extra stability at some reaction intermediate, and/or interfere sterically, allowing an alternate reaction mode. In all of these reactions the products isolated arise by reaction of the quinone methide with the 5–6 double bond of the substrate. No products were isolated by reaction of the quinone methide with either a thione function, or the imine function in compound **11**. This is surprising in view of the known reactivity (16) of the thione function to electrophilic and nucleophilic reagents, but it may be that steric effects are very important. In the one case studied, **5***e*, where the uracil has a *C*-methyl substituent and the 4-thione function, the reaction takes an entirely different course.

Experimental

Chromatography was performed on 1 mm thick "Camag" silica gel type D.S.F. 5 supplied by Terochem Laboratories. The ir spectra were obtained on a Perkin-Elmer model 337 spectrophotometer and nmr spectra on a Varian model 56/60 A spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained on a Finnegan 1015 quadruple mass spectrometer and melting points obtained on a precalibrated "Thermopan" apparatus. Microanalyses were performed by Micro-Tech Laboratories, Inc. and are given in Table 1.

Preparation of the Spirodimer (4)

1-Dimethylaminomethyl-2-naphthol (5.0 g) was refluxed with xylene (150 mL) under nitrogen until there was no further evolution of dimethylamine. The solvent was removed under reduced pressure on a rotary evaporator and the residue chromatographed on a silica gel column. Elution with benzene followed by a mixture of benzene/chloroform (1 : 1, v/v) gave the spirodimer (4.0 g) in 51.5% yield. It was crystallized from a mixture of methanol/ether, mp 142–143°C identical with an authentic specimen (2*b*).

Preparation of 1,3,6-Trimethyl-4-thiouracil (5e)

1,3,6-Trimethyluracil (15) (2 g) was refluxed with phosphorus pentasulfide (2 g) in dry toluene for 7 h. Toluene was removed under reduced pressure and the residue was treated with 10% sodium carbonate solution. The basic solution was extracted with chloroform (25 mL × 4) and the combined organic extract was dried over anhydrous magnesium sulfate. The organic solvent was removed and the residue (2.1 g) crystallized from benzene, mp 172–173°C. The nmr spectrum in $CDCl_3$, δ : 6.57 (s, 1H, olefinic proton), 3.4 (s, 3H, N—CH_3), 3.75 (s, 3H, N—CH_3), 2.18 (s, 3H, C—CH_3). The infrared spectrum: 1685 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 170; found: M^+ 170. *Anal.* calcd. for $C_7H_{10}N_2OS$: C 49.41, H 5.88, N 16.47, S 18.82; found: C 49.14, H 5.99, N 16.25, S 19.10.

General Method for Chroman Synthesis

The uracil or thiazine derivative under study (2 mmol) was treated with an excess of the spirodimer **4** (4 mmol) in refluxing pure, dry mesitylene (25 mL) for 7–8 h under nitrogen. Stirring was maintained throughout the course of reaction and, after the stated reaction time, the organic solvent was removed under reduced pressure. The residue was chromatographed over silica gel to separate the desired adduct from the starting material and other minor by-products. The adducts were then crystallized from chloroform or a mixture of chloroform and benzene for further purification. The results are summarized in Table 1.

Reaction of 1,3-Dimethyluracil (5a) with Spirodimer 4

The reaction was performed as above, and chromatography using chloroform as an eluant gave chroman **7***a* (332 mg) and the phenol **8***a* (156 mg). They were further purified by crystallization from a mixture of chloroform and benzene. The nmr spectrum of chroman **7***a* in $CDCl_3$, δ : 3.17 (s, 3H, *N*-methyl), 3.27 (s, 3H, *N*-methyl), 3.29 (d, 2H, methylene protons), 3.8–4.3 (m, 1H, methine proton), 5.15 (d, J = 2.5 Hz, 1H, methine proton), 6.88–7.98 (m, 6H, aromatic protons). The infrared spectrum: 1685 and 1720 (shoulder) cm^{-1}, C=O stretch. Mass spectrum, calcd.: 296; found: M^+ 296. The nmr spectrum of the phenol **8***a* in $CDCl_3$ and CD_3OD, δ : 3.06 (s, 3H, *N*-methyl), 3.25 (s, 3H, *N*-methyl), 3.92 (d, J = 1.8 Hz, 2H, methylene protons), 6.68 (d, J = 1.8 Hz, olefinic proton), 6.8–8.0 (m, 6H, aromatic protons). The infrared spectrum: 3300 cm^{-1}, OH; 1665 and 1712 cm^{-1}, C=O; 1625 cm^{-1}, C=C stretch. Mass spectrum, calcd.: 296; found: M^+ 296.

Thermolysis of Chroman (7a) with Mesitylene

Chroman (100 mg) was refluxed with pure, dry mesitylene

TABLE 1. Reactions of *o*-quinone methides with uracils and thiazines

Compound	Reference	Product	Yield(%)	Melting point (°C)	Formula	Analysis (%) Calculated C	H	N	S	Found C	H	N	S
5*a*	14	**7***a*	56	208–209	$C_{17}H_{16}N_2O_3$	68.91	5.40	9.46	—	68.79	5.37	9.45	—
5*a*	14	**8***a*	26	254–255	$C_{17}H_{16}N_2O_3$	68.91	5.40	9.46	—	68.92	5.54	9.35	—
5*b*	12	**7***b*	73.9	235–236	$C_{17}H_{16}N_2O_2S$	65.38	5.12	8.97	10.25	65.30	5.21	8.97	10.19
5*c*	12	**7***c*	79.8	222–223	$C_{17}H_{16}N_2O_2S$	62.19	4.87	8.53	19.51	62.14	4.96	8.52	18.81
5*d*	15	**7***b*	56	206–207	$C_{18}H_{18}O_3N_2$	69.67	5.80	9.03	—	69.57	5.87	8.95	—
5*d*	15	**9**	14	203–204	$C_{18}H_{18}O_3N_2$	69.67	5.80	9.03	—	69.83	5.90	9.06	—
6*a*	13	**10***a*	71.9	228–229	$C_{15}H_{11}NO_2S_2$	59.80	3.65	4.65	21.26	59.52	3.71	4.73	21.04
6*b*	13	**10***b*	75	212–213	$C_{16}H_{13}NO_2S_2$	60.95	4.12	4.44	20.31	61.20	4.18	4.73	20.36
11	13	**7***e*	60	186–187	$C_{16}H_{13}NO_2S_2$	60.95	4.12	4.44	20.31	61.17	4.14	4.32	20.27

(10 mL) under nitrogen for 14 h. Mesitylene was removed under reduced pressure and the residue chromatographed over a silica gel plate. Elution of the plate with a mixture of chloroform/benzene (9:1) gave starting spirodimer (1.5 mg), 1,3-dimethyluracil (3 mg), and 1,1-ethylenedi-2-naphthol (1 mg), mp 252°C (lit. (17) mp 252°C), along with a large amount of resinous material and some minor unidentified products.

*Reaction of 1,3-Dimethyl-4-thiouracil (5*b*) with Spirodimer 4*

Chromatography of the reaction mixture using chloroform containing 0.5% methanol gave the phenol **8***b* (461 mg). The phenol was crystallized from chloroform for further purification. The nmr spectrum in acetone-d_6, δ: 3.17 (s, 3H, *N*-methyl), 3.8 (s, 3H, *N*-methyl), 4.37 (d, J = 1.8 Hz, 2H, methylene protons), 6.62 (d, J = 1.8 Hz, 1H, olefinic proton), 7.0–8.0 (m, 6H, aromatic protons). The infrared spectrum: 3300 cm^{-1}, OH; 1710 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 312; found: M^+ 312.

*Reaction of 1,3-Dimethyl-2,4-dithiouracil (5*c*) with Spirodimer 4*

Chromatography of the reaction mixture with chloroform gave the phenol **8***c* (524 mg). It was crystallized from a mixture of chloroform and benzene for further purification. The nmr spectrum in acetone-d_6, δ: 3.6 (s, 3H, *N*-methyl), 4.38 (s, 3H, *N*-methyl), 4.44 (d, J = 1.8 Hz, 2H, methylene protons), 6.90 (d, J = 1.8 Hz, 1H, olefinic proton), 7.18–8.00 (m, 6H, aromatic protons). The infrared spectrum: 3300 cm^{-1}, OH; 1630 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 328; found: M^+ 328.

*Reaction of 1,3,6-Trimethyluracil (5*d*) with Spirodimer 4*

Chromatography of the reaction mixture in chloroform gave the chromans **7***b* (348 mg) and **9** (87 mg). These were crystallized from a mixture of chloroform and benzene for further purification. The nmr spectrum of chroman **7***b* in $CDCl_3$, δ: 1.73 (s, 3H, *C*-methyl), 3.1 (s, 3H, *N*-methyl), 3.2 (s, 3H, *N*-methyl), 2.8–3.68 (m, 3H, methylene and methine protons), 7.0–8.0 (m, 6H, aromatic protons). The infrared spectrum: 1722 and 1670 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 310; found: M^+ 310. The nmr spectrum of the isomeric chroman **9** in $CDCl_3$, δ: 2.3 (s, 3H, *C*-methyl), 3.23 (s, 2H, methylene protons), 3.33 (s, 3H, *N*-methyl), 3.40 (s, 3H, *N*-methyl), 4.13 (s, 1H, methine proton), 6.9–8.0 (m, 6H, aromatic protons). The infrared spectrum: 1705 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 310; found: M^+ 310.

*Reaction of 1,3,6-Trimethyl-4-thiouracil (5*e*) with Spirodimer 4*

The reaction mixture formed an insoluble product in mesitylene. It was removed by filtration (550 mg). It is insoluble in most organic solvents. Its structure is under investigation.

Chromatography of the filtrate in chloroform gave only the starting materials in small amounts.

*Reaction of 1,3-Thiazine-2-thione (6*a*) with Spirodimer 4*

Chromatography of the reaction mixture in chloroform gave the chroman **10***a* (433 mg). It was crystallized from a mixture of benzene and chloroform for further purification. The nmr spectrum in DMSO-d_6 and $CDCl_3$, δ: 5.75 (d, J = 2.5 Hz, 1H, methine proton), 6.9–8.1 (m, 6H, aromatic protons). Since the signals due to the methylene and other methine protons (δ 3.75–3.0) were overlapped by the DMSO and water, their assignments could not be made. The infrared spectrum: 1700 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 301; found: M^+ 301.

Reaction of N*-Methyl-1,3-thiazine-2-thione (6*b*) with Spirodimer 4*

Chromatography of the reaction mixture in benzene gave the chroman **10***b* (473 mg). It was crystallized from benzene for further purification. The nmr spectrum in $CDCl_3$, δ: 3.7 (s, 3H,

N-methyl), 3.0–4.24 (m, 3H, methylene and methine proton), 5.33 (d, J = 2.5 Hz, 1H, methine proton), 6.9–8.1 (m, 6H, aromatic protons). The infrared spectrum: 1710 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 315; found: M^+ 315.

Reaction of 2-Methylthio-1,4-dihydro-1,3-thiazine-4-one (11) with Spirodimer 4

Chromatography of the reaction mixture in chloroform yielded the chroman **12** (378 mg). It was crystallized from benzene for further purification. The nmr spectrum in $CDCl_3$, δ: 2.60 (s, 3H, *S*-methyl), 3.15–3.76 (m, 3H, methine and methylene protons), 5.85 (d, J = 2.5 Hz, 1H, methine proton), 6.9–8.0 (m, 6H, aromatic protons). The infrared spectrum: 1705 cm^{-1}, C=O stretch. Mass spectrum, calcd.: 315; found: M^+ 315.

Acknowledgments

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1. S. PATAI (*Editor*). The chemistry of the quinonoid compounds. Vol. 2. John Wiley, New York. 1974. p. 1145.
2. (*a*) M. S. CHAUHAN, F. M. DEAN, S. McDONALD, and M. L. ROBINSON. J. Chem. Soc. Perkin Trans. I, 359 (1973); (*b*) M. S. CHAUHAN, F. M. DEAN, D. MATKIN, and M. L. ROBINSON. J. Chem. Soc. Perkin Trans. I, 120 (1973); (*c*) N. D. EPIOTIS. J. Am. Chem. Soc. **94**, 1924 (1972); **94**, 1935 (1972).
3. S. B. CAVITT, H. SARRAFIZADEH, and P. D. GARDNER. J. Org. Chem. **27**, 1211 (1962).
4. K. JULTZSCH. J. Prakt. Chem. **158**, 275 (1941); **159**, 180 (1941); Angew. Chem. **60**, 170 (1948); H. EULER, E. ADLER, and J. O. CEDWALL. Arkiv Kemi, **14A**, 1 (1941).
5. J. BRUDIGOU and H. CHRISTOL. C. R. Acad. Sci. **256**, 3149 (1963); **256**, 3323 (1963).
6. A. H. COOK, J. DOWNER, and B. HORNUNG. J. Chem. Soc. 502 (1941).
7. D. SHIRLEY and W. C. SHEEHAN. J. Am. Chem. Soc. **77**, 4606 (1955).
8. P. W. CLUTTERBUCK and J. B. COHEN. J. Chem. Soc. **123**, 2507 (1923).
9. R. N. SEN and N. N. SARKAR. J. Am. Chem. Soc. **47**, 1079 (1925).
10. R. FOSSE, P. DE GRAEVE, and P. E. THOMAS. C. R. Acad. Sci. **200**, 1450 (1935); **201**, 105 (1935).
11. D. A. SULTANOVA. Mater. Nauchn. Konf. Aspirantov, Azerb. Gos. Univ. 83 (1964); Chem. Abstr. **64**, 17,505d (1966).
12. D. J. BROWN and J. S. HARPER. J. Chem. Soc. 1298 (1961).
13. E. N. CAIN and R. N. WARRENER. Aust. J. Chem. **23**, 51 (1970); R. N. WARRENER and E. N. CAIN. Chem. Ind. 1989 (1964).
14. D. DAVIDSON and O. BAUDISCH. J. Am. Chem. Soc. **48**, 2379 (1926).
15. R. BEHREND and R. THURM. Ann. **323**, 165 (1902).
16. R. MAYER. Synthesis and properties of thiocarbonyl compounds. *In* Organosulfur chemistry. *Edited by* M. J. Janssen. Interscience, New York. 1967.
17. R. PUMMERER and E. CHERBULIEZ. Ber. **52**, 1392 (1919).