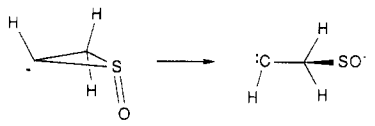
Scheme V



VIII

tronic with ring opening in cyclopropyl anion, which proceeds in a conrotatory manner as a result of the conservation of orbital symmetry.[18]

Both these interpretations explain why *trans*-ethenesulfenate is produced from the syn carbanion (via the transition structure shown in Figure 4a) and *cis*-ethenesulfenate is produced from the anti carbanion (via the transition structure shown in Figure 4b). The higher barrier for the anti carbanion ring opening can be rationalized by considering the secondary overlap in the $\sigma \rightarrow \pi_3$ transformation. For the syn carbanion, the oxygen rotates away from the CH_2 group. However, for the anti carbanion the oxygen rotates toward the CH_2 group, and there is an antibonding interaction between the oxygen and the CH_2 group (indicated by a heavy dashed line in Figure 7b).

The calculations discussed above refer to ring opening by β-elimination. Ring opening could also occur via α-elimination yielding the isomeric carbenic structure (Scheme V). In a MINDO/3 study of three-member rings and their isomers, Dewar and Ramsden[19] found that the acyclic carbenes either rearrange to the corresponding antiaromatic heterocycles without activation or are unstable and collapse without activation to the heterocumulenes (1,2 shift). Imposing a geometry constraint to prevent rearrangement, they found the carbenes to be 17 to 21 kcal/mol less stable than the corresponding heterocycle. Our ab initio calculations are in agreement with these results, since several attempts to optimize structures like VIII at the STO-3G* level resulted in the reclosure to the original cyclic carbanion. Recent experimental results with appropriately deuteriated episulfoxides also discount ring opening via α-elimination.[3b]

(18) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie-Academic: 1970.
(19) Dewar, M. J. S.; Ramsden, C. A.; *J. Chem. Soc., Chem. Commun.* 1973, 688.

Conclusions

The ab initio calculations on the syn and the anti carbanions obtained for the model system, ethene episulfoxide, indicate the following: 1. The two carbanions show about the same relative stability. 2. The activation energy for the ring-opening process is significantly lower for the syn carbanion. The possible interaction with Li cation would also favor the formation and opening of the syn form. Substituent effects in the experimentally studied compounds should act in the same direction. 3. The inversion barrier for the conversion of the anti carbanion to the syn is comparable to the barrier to ring opening, and thus accounts for the partial loss of stereospecificity. Considering the effect of substituents on inversion barriers, this process should be easier for the phenyl substituted episulfoxides studied experimentally and would enhance the partial loss of stereospecificity in the trans-disubstituted compound. Chelation of Li^+ would also increase the loss of stereospecificity by favoring the formation of the syn carbanion. 4. An alternative ring-opening pathway leading to loss of stereospecificity has been shown to be very unlikely. 5. The possibility of ring opening via α-elimination can be ruled out, in accord with experimental findings. The products would be carbenic structures which are unstable with respect to reclosure of the ring.

Acknowledgment. We thank Professor R. D. Bach (Wayne State University) and Dr. C. Paolucci (University of Bologna) for helpful discussions. Grants from the Ministero della Pubblica Istruzione, the National Science Foundation (CHE-83-12505), and NATO (RG096.81) are gratefully acknowledged.

Registry No. Ethene episulfoxide carbanion, 110224-75-4; ethylene episulfoxide, 7117-41-1; ethenesulfenate anion, 110224-76-5.

Diisophorone and Related Compounds. 20.[1] Diisophoranes Incorporating the 1,3-Thiazine Ring System: 8,11a-Methanocycloocta[*d*,*e*][3,1]benzothiazines

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S-(Diisophor-2(7)-en-1-yl)isothioureas **3–6** are obtained by the interaction of 1-chloro(or hydroxy)diisophor-2(7)-ene (**1**, **2**) with thiourea or its mono- or 1,1- or 1,3-disubstituted homologues and yield diisophor-2-(7)-ene-1-thiol (**7**) on treatment with alkali. In the case of 1-chloro(or hydroxy)diisophor-2(7)-en-3-ones (**12**, **13**), the same group of reactions is attended by simultaneous intramolecular cyclodehydration, resulting in 8,11a-methanocycloocta[*d*,*e*][3,1]benzothiazines **16–23**.

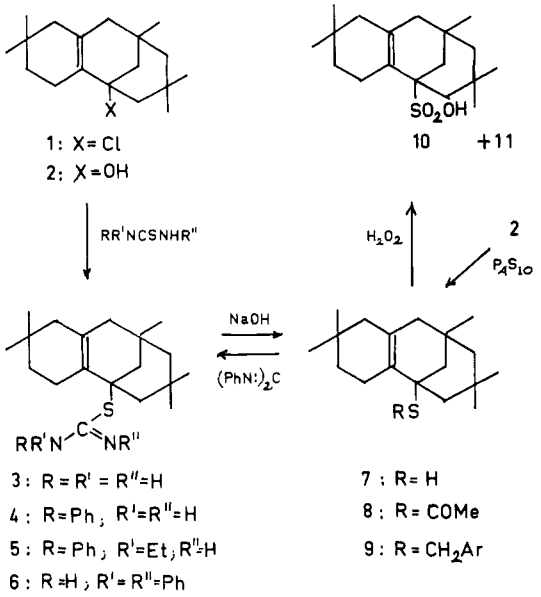
Introduction

One of the more striking properties of the three-dimensional structure of diisophorone (e.g., **12**) is the readiness with which an additional six- or seven-membered ring D may be attached to the molecule so as to incorporate carbon atoms C-1, C-2, and C-3 of the original carbon skeleton. The formation of such structures by replacement–elimination processes at C-1 and C-3 is exemplified by the condensation of the parent β-ketol **13** with ethane-1,2-diol to dioxepanes **A**[2] or with another molecule of

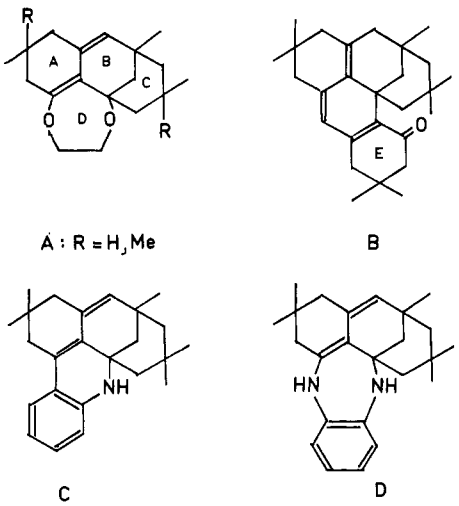
(1) Part 19: Kurzer, F.; Mitchell, J. B. O.; Patel, J. N. *Monatsh. Chem.*, in press.
(2) Furth, B.; Kossanyi, J.; Morizur, J. P.; Vandewalle, M. *Bull. Soc. Chim. Fr.* 1967, 1428.

0022-3263/87/1952-4966$01.50/0

Scheme I



isophorone to the pentacyclic keto triene **B**.[3] We have previously described the facile cyclodehydration of 1-anilinodiisophor-2(7)-en-3-ones to the fused pentacyclic structures **C**, and the formation of a seven-membered analogue (**D**) by the interaction of **12** and 1,2-diaminobenzene.[4] We now report the synthesis of novel tetracyclic structures incorporating the 1,3-thiazine ring system, by the condensation of diisophorones and thioureas.



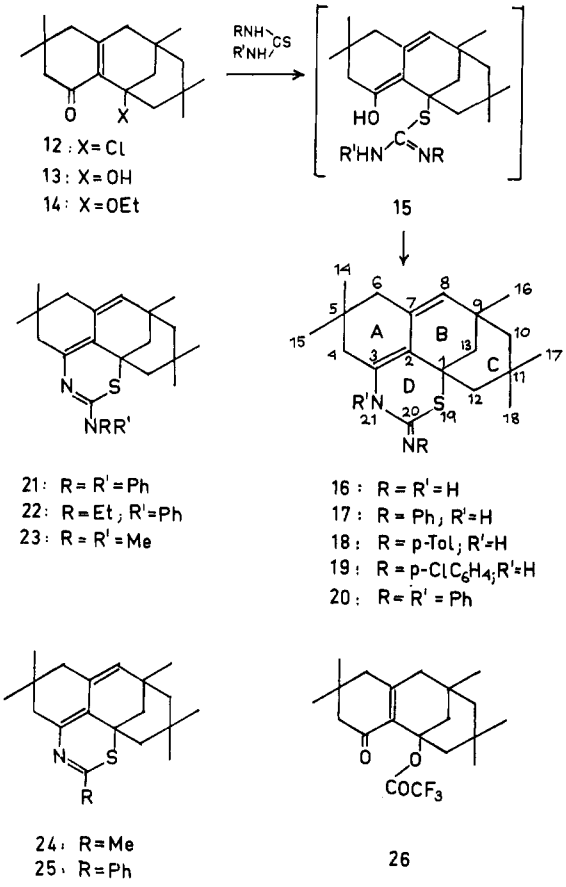
A brief introductory account of the production of diisophor-2(7)-ene-1-thiol by way of *S*-(diisophor-2(7)-en-1-yl)isothiuronium salts is relevant to the formulation of the condensed structures: Because of the possible alternative modes of the interaction of the bifunctional thioureas with the 1-hydroxy 3-ketone **13** or 1-chloro 3-ketone **12**, their action pattern at the 1-bridgehead was first established by using a diisophorane model devoid of substituents elsewhere.

Results and Discussion

1-*S*-Isothioureidodiisophoranes. Thus, the interaction of 1-chlorodiisophor-2(7)-ene (**1**) and thiourea in trifluoroacetic acid readily gave *S*-(diisophor-2(7)-en-1-yl)isothiourea (**3**) (Scheme I), isolated as the isothiuronium trifluoroacetate. The use of 1-mono-, 1,1-di-, and 1,3-disubstituted thioureas similarly afforded the corresponding expected[5] *S*-isothioureas **4–6** in high yield. The disubstituted examples **5** and **6** were isolable as the free bases, in accord with the established stabilization of isothioureas with increasing number of N-substituents.[6] The formulation of the *S*-isothioureidodiisophorenes **3–6** suggested by the conversion of the prototype **3** by alkali into diisophor-2(7)-ene-1-thiol (**7**), was confirmed by the unequivocal synthesis of the *N,N'*-diphenyl analogue **6** by the addition of diphenylcarbodiimide to this thiol (**7** → **6**).

The identity of diisophor-2(7)-ene-1-thiol (**7**) with material produced from diisophor-2(7)-en-1-ol (**2**) by direct thiolation using phosphorus pentasulfide[7] further confirmed its structural assignment. The IR spectrum of **7** includes the usual alicyclic methyl and methylene peaks but is otherwise featureless; the weak absorptions at 1310 and 845 cm^{-1} are not characteristic of a thiol group,[8] the only function in the molecule, and cannot be so assigned.

Scheme II[a]



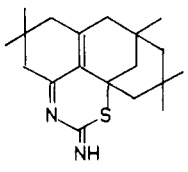
[a] Compounds **16–19** (R' = H) assume, at least in solution, the tautomeric 20-amino structure, in line with that of **21–23**.

(3) Bertrand, J. A.; Cheung, B.; Hammerich, A. D.; House, H. O.; Reichle, W. T.; Vanderveer, D.; Zaiko, E. J. *J. Org. Chem.* **1977**, *42*, 1600.
(4) Allen, A. A.; Kurzer, F. *Monatsh. Chem.* **1981**, *112*, 769.
(5) Bögemann, M.; Petersen, S.; Schultz, O. E.; Söll, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Thieme: Stuttgart, 1955; Vol. IX, p 900.
(6) *Beilstein's Handbuch der Organischen Chemie*, 4th ed.; Springer: Berlin, 1918; (Me homologues) Vol. 3, p 192; Vol. 4, Suppl. 1, pp 334, 338; (Et homologues) Vol. 3, p 192; Vol. 4, Suppl. 1, pp 124, 355 and later Supplements. Delépine, M. *Bull. Soc. Chim. Fr.* **1910**, *7*, 993; *Ann. Chim.* **1912**, *25*, 559.
(7) Beckmann, E. O. *J. Prakt. Chem.* **1878**, *17*, 439. Schlesinger, R. H.; Schultz, A. G. *J. Am. Chem. Soc.* **1968**, *90*, 1676. Weinstraub, P. M. *Int. J. Sulfur Chem.* **1973**, *8*, 321.
(8) Dolphin, D.; Wick, A. *Tabulation of Infrared Spectral Data*; Wiley-Interscience: New York, 1977; p 22. Cross, A. D.; Jones, R. A. *An Introduction to Practical Infrared Spectroscopy*; Butterworth: London, 1969; p 94.

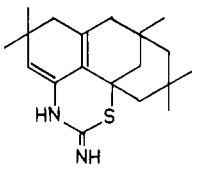
The liquid thiol **7** was further characterized as its crystalline *S*-acyl derivatives **8** and **9**. Its oxidation by alkaline hydrogen peroxide[9] gave, as the main product, the 1-sulfonic acid **10** (isolated as the *S*-benzylisothiuronium salt), together with small yields of the disulfide **11** (not shown in Scheme I), arising by the linking of two molecules of the thiol. The close resemblence of the IR spectra of **11** and its precursor thiol **7** is noteworthy; the formulation of **10** is in accord with the appearance of intense peaks attributable[8] to its sulfonic acid grouping.

Condensed 1,3-Thiazinodiisophorones. In the interaction of diisophor-3-ones **12–14** with thioureas, both the 3-keto and 1-bridgehead functions participate in the condensation, resulting in the fusion of a 1,3-thiazine ring with the original structure. Thus, 1-chlorodiisophor-2-(7)-en-3-one (**12**) and thiourea reacted in boiling formic or trifluoroacetic acid to yield, by a simultaneous dehydrohalogenation and cyclodehydration, a product formulated as **16** (Scheme II). 1-Chloro-5,11-bisnordiisophor-2(7)-en-3-one[10] gave the corresponding lower homologue.

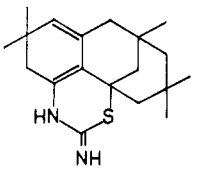
The structural assignment to the novel tetracyclic products is based on their origin, composition, and properties. The proposed disposition of ring D with its sulfur atom linked to C-1 takes account of the preferred S-alkylation of thioureas in the case of the 3-deketodiisophorenes (see above). The presence of one doublet and five triplets in the carbon NMR spectrum of **16** excludes the isomeric azine-like structure **16a** but does not prohibit the homoannular diene variants **16b** and **16c**. Their



16a



16b

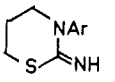


16c

differentiation by the position of the UV absorption maximum is also unavailable, since the Woodward–Fieser–Scott rules,[12] serviceable in the case of the tricyclic diisophorones,[4,13] are inapplicable to the extended heterocyclic structures. In conformity with precedents,[13] the heteroannular distribution of the conjugated diene system (as in **16**) is adopted throughout (**17–23**), a choice that is supported by the small upfield displacement of the 17-methyl ^{13}C quartet associated with the compounds concerned (**16**, **17**, **20**; $\delta_{C\text{-}17}$ from the usual[14] 33 to 31 ppm); this shielding effect has been traced to the spatial proximity of the 17-methyl group opposite the heteroannular 2,7-diene system in precedents of established structure.[13-15]

The tetracyclic prototype **16** is basic, forming salts with strong acids and yielding a monobenzoyl derivative. It is conveniently isolated as the trifluoroacetate, from which the free base is liberated by alkali. Continued action of boiling alkali has no effect, in accord with the established resistence of benzo-1,3-thiazine to ring-opening by acids and alkalis.[16]

Analogues of **16** incorporating alkyl and aryl groups in their 1,3-thiazine ring were accessible in moderate to good yields by the use of substituted thioureas. The structure of examples arising from 1,3- and 1,1-disubstituted thioureas are attributable unequivocally by their origin (as **20** and **21–23**, respectively), as are those of analogues (**24**, **25**) derived from thioamides. Those obtained from 1-monoarylthioureas are formulated as **17–19** (or tautomers) on the assumption that the cyclodehydration of the intermediate isothioureas **15** (R′ = H, R = Ar) involves their free amino rather than their arylamino group. However, the alternative ring-closure is not absolutely ruled out, because in a synthesis of 1,3-thiazines by the condensation of 1,3-dihalogenopropanes and 1-arylthioureas, the ring-arylated H rather than the 2-arylamino isomers are obtained.[17] The formulation here adopted (**17–19**) receives some independent support from the carbon NMR spectral data (see below).



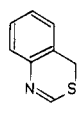
H

Further structural details are inferred from the fact that the UV spectra of all the tetracyclic compounds (**16–23**, except **20**), featuring three prominent absorption maxima, resemble one another closely in outline: a case may thus be made for the preferred conjugated distribution of the unsaturated centers in compounds **16–19** (where R′ = H) as in their *N*,*N*-disubstituted analogues (**21–23**), in which the presence of the fully conjugated triene system is mandatory. Where this triene pattern is prohibited (as in **20**), a simpler spectrum, displaying a hypsochromic shift of its main absorption (from ca. 325–335 to 306 nm) reflects the less extended conjugation.

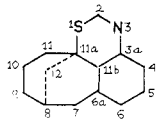
Mechanism. The first stage of the condensation (e.g., **12** → **16**) is thought to be the displacement of the 1-bridgehead substituent (in **12–14**) by the usual[18] S_N1 mechanism, resulting in intermediates of type **15**; in the case of the diisophor-2(7)-enes (**1**, **2**) lacking the 3-keto function, reaction terminates at this point. The involve-

(9) Procedure: Buchman, E. R.; Reims, A. O.; Sargent, H. *J. Org. Chem.* **1941**, *6*, 764.

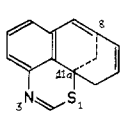
(10) **Nomenclature**: The IUPAC nomenclature bases the name of the present structures (e.g., **16**) ultimately on their fully unsaturated heterocyclic parent hydrocarbon, [3,1]-benzothiazine (E), and thence on the



E



F



G

fully conjugated parent structure G, from which the name is immediately derived. Since the result (e.g., 2,3,4,5,6,8,9,10,11,11a-decahydro-2-imino-5,5,8,10,10-pentamethyl-8,11a-methanocycloocta[*d*,*e*][3,1]benzothiazine for **16**), though indispensible for data retrieval, is unwieldy we extend our simplified nomenclature[1,4,11] to the present structures, with retention of the usual numbering of the ring system (see **16–20**), for ease of comparison between this and previous series of compounds. The "3,21-dehydro" component of the names reflects the relation of the products to their 1-*S*-thioureido-3-keto precursors **15**. International Union of Pure and Applied Chemistry: *Nomenclature of Organic Chemistry*; Rigaudy, J., Klesney, S. P., Eds.; Butterworth: London, 1979. *Chemical Abstracts Index Guide, 1972–1976*; Chemical Abstract Service: Columbus, 1977; Vol. 76–85, p 1171 et seq.

(11) Allen, A. A.; Duffner, C. R.; Kurzer, F. *Tetrahedron* **1978**, *34*, 1247. Kurzer, F.; Morgan, A. R.; Rettig, S. J. *Monatsh. Chem.* **1984**, *115*, 333.

(12) Dannenberg, H. *Abh. Preuss. Akad. Wiss.* **1939**, *21*, 3. Woodward, R. B. *J. Am. Chem. Soc.* **1941**, *63*, 1123; **1942**, *64*, 76. Dorfman, L. *Chem. Rev.* **1953**, *53*, 47. Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 15–21. Scott, A. I. *Interpretation of the Ultraviolet Spectra of Natural Products*; Pergamon: Oxford 1964; pp 46, 58, 74, 79.

(13) Kurzer, F.; Morgan, A. R. *Monatsh. Chem.* **1981**, *112*, 129. Allen, A. A.; Kurzer, F. *Ibid.* **1985**, *116*, 777.

(14) Davies, P. R.; Morgan, A. R.; Kurzer, F. *Monatsh. Chem.* **1983**, *114*, 739.

(15) Kurzer, F.; Patel, J. N. *Monatsh. Chem.*, in press.

(16) Bourgoin-Legay, D.; Bourdet, R. *Bull. Soc. Chim. Fr.* **1969**, 2524.

(17) Glasser, A. C.; Doughty, R. M. *J. Pharm. Sci.* **1965**, *54*, 1055. Toldy, L.; Sohar, P. *Tetrahedron Lett.* **1970**, 181. Toldy, L.; Sohar, P.; Farago, K.; Toth, I.; Bartalits, L. *Ibid.* **1970**, 2167.

(18) Buchanan, G. L. In *Topics in Carbocyclic Chemistry*; Lloyd, D., Ed.; Logos: London, 1969; pp 199, 223.

Table I. Carbon-13 NMR Spectra of S-Substituted Diisophor-2(7)-enethiols 8 and 5 and Tetracyclic Condensation Products 16–22 (All in $CDCl_3$)

C	8	5	16	17	22	20
C-1	57.6 s	56.1 s	47.1 s	47.1 s	47.0 s	44.9 s
C-2	128.3 s	128.9 s	132.3 s	131.9 s	132.7 s	131.5 s
C-3	24.2 t	24.0 t	112.5 s	112.0 s	111.9 s	118.7 s
C-4	45.0[g] t	46.0[g] t	45.3[g] t	44.0[g] t	45.9[g] t	43.1[g] t
C-5	31.8[h] s	31.9[h] s	30.0[h] s	30.0[h] s	30.2[h] s	30.4 s
C-6	44.5[g] t	45.3[g] t	44.2[g] t	43.8[g] t	44.3[g] t	44.0[g] t
C-7	131.3 s	135.2 s	140.8 s	135.3 s	141.6 s	133.5 s
C-8	36.1 t	36.0 t	130.5 d	130.1 d	129.6 d	131.0 d
C-9	31.4[h] s	31.3[h] s	34.2 s	34.4 s	34.2 s	34.2 s
C-10	52.8 t	52.9 t	52.3 t	52.6 t	51.7 t	52.1 t
C-11	29.1 s	29.2 s	32.0[h] s	32.0[h] s	31.9[h] s	32.2 s
C-12	44.0[g] t	44.0[g] t	50.5 t	50.3 t	50.9 t	49.7 t
C-13	45.7[g] t	46.4[g] t	46.9 t	46.7 t	46.9 t	46.5 t
C-14	31.1 q	29.2 q	27.0 q	27.4 q	27.2 q	25.9 q
C-15	31.6 q	31.6 q	28.9 q	29.0[i] q	29.1 q	28.8 q
C-16	28.8 q	26.2 q	30.1 q	29.7[i] q	30.3[i] q	30.4 q
C-17	33.0 q	33.0 q	30.7 q	30.7 q	30.8[i] q	30.7 q
C-18	37.4 q	37.3 q	37.1 q	37.0 q	37.1 q	36.9 q
C-19	195.8 s[a]	160.1 s				
C-20	24.9 q[b]	45.3[g] t[c]	152.4 s	150.8 s	151.7 s	151.1[h] s
C-21		12.8 q[d]			46.1 t	
C-22					13.2 q	
C-1′		143.3 s		144.7 s	143.2 s	141.0 s
C-2′		128.9 d[e]		121.6 d[e]	128.9 d[e]	122.2 d[e]
C-3′		129.7 d[e]		128.7 d[e]	128.9 d[e]	128.6 d[e]
C-4′		127.0 d		123.3 d	127.0 d	122.7 d
C-1″[f]						150.0[h] s
C-2″[f]						128.2[i] d[e]
C-3″[f]						129.6[i] d[e]
C-4″[f]						127.1 d

[a] Carbonyl carbon. [b] Acetyl methyl carbon. [c] Methylene carbon of ethyl. [d] Methyl carbon of ethyl. [e] Signal of double intensity. [f] Benzene ring on N-21. [g,h,i] Signals may be interchanged vertically.

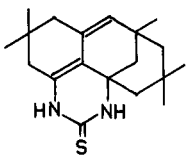
ment of diisophor-2(7)-ene carbonium ions in the process is in further accord with the observations that the 1-hydroxy and 1-ethoxy analogues of the 1-chlorodiisophorones are equally suitable starting materials in this condensation (**12**, **13**, **14** → **17**; also **1**, **2** → **3**), while 1-carboxydiisophor-2(7)-en-3-one, being incapable of furnishing 1-carbonium ions under the prevailing conditions,[11,19] fails to react.

Reaction is completed by the acid-catalyzed intramolecular cyclodehydration between the most reactive *S*-isothioureaamino group and the 3-keto function (in **15**).

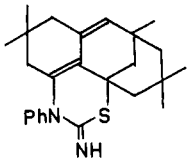
[However, in contrast to the stability of the *S*-diisophor-2(7)-en-1-ylisothioureas **3–6**, the postulated intermediate 3-keto analogues **15** were not isolable. Under restrained conditions (e.g., boiling ethanol), the action of thiourea on **12** resulted in the cyclized product **16** directly, while phenylthiourea failed to react entirely. *N,N,N′*-Trisubstituted thioureas, the action of which on **12** would necessarily terminate at the 1-substitution stage, were recovered even after prolonged interaction in boiling trifluoroacetic acid: the resulting 1-trifluoroacetyl compound **26** arose by a replacement that was effected by the acid medium alone.]

Carbon NMR Spectra. The spectra of representative structures are displayed in accordance with their proposed assignment in Table I. The reasoning previously detailed for interpreting the spectra of diisophorones[14,20] is applicable in its essentials to the present examples; the brief comments on the new spectral data are therefore confined to points of structural interest.

Singlets. The 1-bridgehead carbon in **5** and **8** is associated with a singlet resonating at 56–57 ppm, i.e., within the (somewhat wide) limits established[21] for the >C–S– moiety (55–70 ppm). In the spectra of the methanocyclooctabenzothiazines **16**, **17**, **20**, and **22**, this signal appears in the 44–47 ppm range. Several diisophorones incorporating a 1-amino function (including 1-benzamidodiisophor-2(7)-en-3-one, the pentacyclic secondary amines C and D, and others) produce their 1-bridgehead singlet consistently at lower field (53–57 ppm[22]): this divergence thus supports by exclusion the adopted structures **16–22** founded on the chemical evidence. The same data imply the inadmissibility of the isomeric thioureido structure **16d**, and tautomers, which is further discounted by the absence of the low-field thiocarbonyl singlet characteristic of both linear[23,24] (177–194 ppm) and alicyclic[24,25] thioureas (180–183 ppm).



16d



17a

In passing from **17** to **20**, the notable spectral change is the downfield displacement (by 7 ppm) of the C-3 singlet. This observation, ascribed to the effect of the new phenyl group in the position close to C-3, supports the formulation of the monophenyl compound (as **17**): the C-3 singlet of

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(20) Kurzer, F.; Patel, J. N. *Monatsh. Chem.* **1984**, *115*, 825.
(21) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden & Son: London, 1978. Chart at end.
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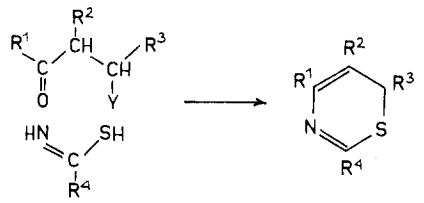
(23) Filleux-Blanchard, M. L. *Org. Magn. Reson.* **1977**, *9*, 125. Arduengo, A. J.; Burgess, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 5021. Arduengo, A. J.; Burgess, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 5021.
(24) Kalinowski, H. O.; Kessler, H. *Org. Magn. Reson.* **1974**, *6*, 305.
(25) Faure, R.; Vincent, E. J.; Assef, G.; Kister, J.; Metzger, J. *Org. Magn. Reson.* **1977**, *9*, 688.

Scheme III



the latter matches in its chemical shift that of the unsubstituted parent model **16** (112.5 ppm) rather than that of **20** (118.7 ppm). This disfavors the alternative structure **17a**, in which the phenyl group in proximity to C-3 would presumably exert an effect comparable to that in **20**.

Other Signals. Absence of the usual 3-keto function of diisophorones (in **5**, **8**) is reflected by the appearance of a new triplet conforming in its chemical shift (24 ppm) to that of methylene groups flanking the double bond in cyclohexenes (ca. 25–26 ppm).[26]

The signals of the exocyclic aromatic groups of all the compounds were identifiable by reference to the assigned carbon NMR spectra of aniline[27] and *N,N*-diethylaniline.[28] In the diphenyl compound **20**, one set of doublets having shieldings coincident with those of the aromatic ring of the monophenyl compound **17** are allocated to the identically placed ring, leaving the remainder for distribution to the phenyl group attached to N-21 (of **20**).

Conclusion. The readiness with which a 1,3-thiazine moiety is fused to the condensed ring system in the present reaction suggests the wider utility of this synthetic approach to 1,3-thiazines in general (Scheme III). Thus, the condensation of β-halogeno ketones with thioamido compounds (R^4 = Alk, Ar, NRR′, OR, SR, etc.) would seem a desirable potential addition to existing 1,3-thiazine syntheses,[29,30] supplementing particularly the established route involving the interaction of β-chloro ketones and nitriles.[30]

Experimental Section

Melting points are uncorrected. Light petroleum had bp 60–80 °C unless otherwise specified. Pyridine was the commercial anhydrous grade.

Carbon magnetic resonance spectra were determined on a Bruker WM 250 Fourier transform instrument operating at 62.89 MHz, with tetramethylsilane as the internal standard. Mass spectra were obtained on an AEI MS-902 instrument at 70 eV. IR spectra were recorded on a Unicam SP 1000 instrument using KBr disks. Unassigned peaks of IR spectra are not listed except for the key compounds **3**, **16**, **17**, and **20**. UV spectra were measured with an SP 800 A spectrophotometer, using ethanolic solutions (ca. 50 mg/L).

Compounds Related to Diisophor-2(7)-ene-1-thiol. *S*-Diisophor-2(7)-en-1-ylisothiourea (3). A solution of 1[31] (1.40 g, 5 mmol) and thiourea (0.42 g, 5.5 mmol) in CF_3CO_2H (10 mL) was boiled under reflux for 5 h and then stirred into ice–water. The precipitated resin was rinsed with H_2O and immediately dissolved in warm MeOH (6 mL). The deposited crystals (mp 189–191 °C; yield 72–80%) gave, on crystallization from the same solvent (recovery, 50%), ivory prisms of **3** trifluoroacetate, mp 190–191 °C: IR 3400, 3300 vs (NH_3^+), 2950–2870 vs, 1465, 1460, 1440 s (CH_3, CH_2), 2770 m (NH_2^+), 1665 vs br (CO), 1390 m, 1370 ms (CMe_2), 1200, 1180, 1140 vs (CF_3COOH), 840 s, 730 s cm^{-1}. Anal. Calcd for $C_{19}H_{32}N_2S{\cdot}CF_3COOH$: C, 58.1; H, 7.6; N, 6.45; S, 7.4; F, 13.1. Found: C, 58.9; H, 7.1; N, 6.2; S, 8.1; F, 13.7. The use of 1-hydroxydiisophor-2(7)-ene[2,31] (**2**, 1.31 g, 5 mmol) gave the same **3** trifluoroacetate, mp 190–191 °C, in 74% yield.

Equimolar quantities of the trifluoroacetate and picric acid in ethanol gave **3** picrate, mp 185–187 °C. Anal. Calcd for $C_{19}H_{32}N_2S{\cdot}C_6H_3N_3O_7$: C, 54.65; H, 6.4; N, 12.75; S, 5.8. Found: C, 54.7; H, 6.4; N, 12.65; S, 5.7.

***S*-5,11-Bisnordiisophor-2(7)-en-1-ylisothiourea.** The use of the 5,11-bisnor homologue of 1[31] (1.25 g, 5 mmol) in the foregoing procedure deposited very slowly the crude trifluoroacetate as a low-melting powder, which could not be crystallized. It was therefore converted in MeOH into the picrate, mp 169–171 °C (from EtOH; yield, 35%). Anal. Calcd for $C_{17}H_{28}N_2S{\cdot}C_6H_3N_3O_7$: C, 53.0; H, 5.95; N, 13.4. Found: C, 53.5% H, 5.7; N, 13.5.

***S*-Diisophor-2(7)-en-1-yl-*N*-phenylisothiourea (4)** was obtained like **3** by the use of phenylthiourea (0.84 g, 5.5 mmol). **4** trifluoroacetate: mp 162–164 °C (from ethanol; yield, 68%); IR 3380 s (NH_3^+), 2950–2860 vs mult, 1475 ms, 1440 ms (CH_3, CH_2), 2700 s (NH_2^+), 1665 vs vbr, 1650 s sh, 1640 s sh (CO), 1200, 1170, 1120 vs (CF_3COOH), 770 m, 715 s (Ph) cm^{-1}. Anal. Calcd for $C_{25}H_{36}N_2S{\cdot}CF_3COOH$: C, 63.5; H, 7.3; N, 5.5. Found: C, 64.0; H, 7.4; N, 5.75. **4** picrate: mp 184–185 °C (from EtOH). Anal. Calcd for $C_{25}H_{36}N_2S{\cdot}C_6H_3N_3O_7$: C, 59.5; H, 6.2; N, 11.2. Found: C, 59.9; H, 6.3; N, 11.0.

***S*-Diisophor-2(7)-en-1-yl-*N*-ethyl-*N*-phenylisothiourea (5).** A solution of **1** (1.40 g, 5 mmol) and *N*-ethyl-*N*-phenylthiourea (1.0 g, 5.5 mmol) in CF_3CO_2H (10 mL) was refluxed for 6 h, the red liquid stirred into H_2O, and the precipitated viscid oil washed with successive portions of H_2O. Dissolution in EtOH (5 mL) and treatment with 3 M NaOH (3.3 mL, 10 mmol) and H_2O (5 mL) precipitated an oil solidifying at 0 °C, giving needles of **5**: mp 124–127 °C (from 80% EtOH; yield, 54%); UV λ_{max} 220 nm (log ε 4.12), 255 (3.69); IR 3320 s (=NH), 2950–2850 vs, 1470, 1465 ms (CH_3, CH_2), 1580 vs (? C=N), 1385 ms, 1365 vs (CMe_2), 1300 vs (NR_3), 790 s, 775 ms, 760 m, 700 vs (Ph), 1500 vs, 1105 vs cm^{-1}. Anal. Calcd for $C_{27}H_{40}N_2S$: C, 76.4; H, 9.4; N, 6.6; S, 7.55. Found: C, 76.3; H, 9.5; N, 6.55; S, 7.7. **5** picrate: prisms; mp 189–191 °C (from 2-ethoxyethanol, yield 60%). Anal. Calcd for $C_{27}H_{40}N_2S{\cdot}C_6H_3N_3O_7$: C, 60.6; H, 6.6; N, 10.7; S, 4.9. Found: C, 60.8; H, 6.8; N, 10.65; S, 4.7.

***S*-Diisophor-2(7)-en-1-yl-*N,N*′-diphenylisothiourea (6).** **(a)** The base **6** was obtained like **5** by use of *N,N*′-diphenylthiourea (1.25 g, 5.5 mmol). The precipitated oil hardened on storage and was treated with MeOH (5 mL): the undissolved solid was unchanged *N,N*′-diphenylthiourea (32%). The filtrate deposited needles (mp 172–175 °C, total 48% based on the thiourea converted), affording **6**: mp 173–175 °C (from MeOH); UV λ_{max} 215 nm (log ε 4.24), 262 (4.10); IR 3350 vs (NH), 2950–2880 vs, 1465, 1440 ms (CH_3, CH_2), 1625, 1595 vs (? C=N), 1395 w, 1370 mw (CMe_2), 770 mw, 750 ms, 745 m t, 695 ms (Ph) cm^{-1}. Anal. Calcd for $C_{31}H_{40}N_2S$: C, 78.8; H, 8.5; N, 5.9; S, 6.8. Found: C, 79.0; H, 8.3; N, 5.8; S, 7.1.

(b) Unequivocal Synthesis. A solution of the thiol **7** (see below, 1.39 g, 5 mmol) and diphenylcarbodiimide (0.97 g, 5 mmol) in anhydrous acetone (20 mL) was refluxed for 1.5 h, the solvent removed, and the remaining resin dissolved in MeOH (15 mL). The liquid deposited successively *N,N*′-diphenylurea (0.20 g) and **6** (total, 48%), identical with material obtained in a.

Diisophor-2(7)-ene-1-thiol (7). A boiling solution of **3** trifluoroacetate (7.8 g, 18 mmol) in EtOH (50 mL) was treated dropwise during ca. 10 min with 5 M NaOH (16 mL, 80 mmol), more EtOH (25–40 mL) being added to maintain a single phase. After 2 h of refluxing, the turbid liquid was distilled to half-volume and treated with 1.5 M HCl (60 mL) and the precipitated oil extracted with ether. Evaporation of the washed (H_2O) and dried (Na_2SO_4) extract, again in the presence of benzene (removal of H_2O), gave a residual oil, which afforded on vacuum distillation thiol **7** as a colorless slightly viscid liquid, of not disagreeable odor, quite uncharacteristic of mercapto compounds (yield, 72–80%): bp 134–136 °C (1.5 mm), 114–117 °C (0.4 mm); n_{22} 1.5230; n_{13} 1.5276; IR (neat) 2950, 2900 vs d–2860 vs, 1460 m br (CH_3, CH_2),

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1390, 1370 m (CMe_2), 1310 w, 845 w cm^{-1}. Anal. Calcd for $C_{18}H_{30}S$: C, 77.7; H, 10.8; S, 11.5; mol wt 278. Found: C, 78.3; H, 10.7; S, 10.8; mol wt (mass spectrometrically) 278.

1-(Acetylthio)diisophor-2(7)-ene (8). (a) A solution of the thiol **7** (1.39 g, 5 mmol) in Ac_2O (12 mL) was boiled for 2 h and then stirred into H_2O (120 mL). The solidified oil, dissolved in MeOH (10 mL), slowly deposited crystals, which gave **8**: mp 65–67 °C (from MeOH yield 58%); IR 2950–2850 vs, 1460, 1435 m (CH_3, CH_2), 1685 vs (CO), 1385 m, 1360, 1350 ms (CMe_2), 1108 s (? C–S, thioester) cm^{-1}. Anal. Calcd for $C_{20}H_{32}OS$: C, 75.0; H, 10.0; S, 10.0. Found: C, 75.1; H, 10.0; S, 9.7.

(b) A solution of **2** (0.79 g, 3 mmol) and phosphorus pentasulfide (1.33 g, 6 mmol) in pyridine (10 mL) was boiled for 2 h and the crimson liquid stirred into ice (100 g)–concentrated HCl (12 mL). The product was isolated by ether extraction and acetylated as in a, giving **8** (yield, 42%), identical with material obtained in a.

1-(Benzylthio)diisophor-2(7)-ene (9, Ar = Ph). A solution of **7** (1.39 g, 5 mmol) in EtOH (8 mL), treated with Na (0.12 g, 5 mmol) in EtOH (5 mL), then H_2O (5 drops) and benzyl chloride (0.63 g, 5 mmol), was refluxed for 30 min. The turbid liquid was distilled to half-volume and stirred into H_2O. The solid (mp 75–80 °C, yield 56–68%) gave **9** (Ar = Ph): mp 80–81 °C (from MeOH) IR 2950–2850 vs, 1460 s (CH_3, CH_2), 1380 m, 1360 ms (CMe_2), 710 s, 695 s (Ph) cm^{-1}. Anal. Calcd for $C_{25}H_{36}S$: C, 81.5; H, 9.8; S, 8.7. Found: C, 81.3; H, 9.3; S, 9.0.

1-[(*p*-Nitrobenzyl)thio]diisophor-2(7)-ene (9, Ar = $C_6H_4NO_2$-*p*) was similarly prepared by the use of *p*-nitrobenzyl bromide (1.62 g, 7.5 mmol), mp 258–260 °C (from DMF; yield, 52%): IR 2950–2850 vs mult, 1455 ms (CH_3, CH_2), 1525 vs, 1345 vs (NO_2), 865 ms, 845 m, 805 m (para-substituted Ar) cm^{-1}. Anal. Calcd for $C_{25}H_{35}NO_2S$: C, 72.6; H, 8.5; N, 3.4; S, 7.75. Found: C, 72.8; H, 7.9; N, 3.7; S, 7.9.

Diisophor-2(7)-ene-1-thiol: Oxidation. A stirred solution of **7** (1.39 g, 5 mmol) in EtOH (15 mL) containing 3 M NaOH (0.4 mL) was treated dropwise at 50 °C during 10–15 min with 30% H_2O_2 (1.7 mL, 15 mmol; containing 3 M NaOH, 0.4 mL), a clear solution being maintained by the addition of more EtOH as necessary (ca. 10 mL). The liquid was kept at 60 °C for 1 h, refluxed for 30 min, and then distilled to half-volume. It slowly deposited solid (filtrate F), which gave **bis(diisophor-2(7)-en-1-yl) disulfide (11)**: mp 174–176 °C (from MeOH, yield 10–15%); IR 2950, 2920 vs, 1465 m, 1460 ms, 1440 m (CH_3, CH_2), 1385 m, 1365 ms (CMe_2), 1305 m, 840 m cm^{-1}. Anal. Calcd for $C_{36}H_{58}S_2$: C, 78.0; H, 10.5; S, 11.55; mol wt 554. Found: C, 77.8; H, 10.2; S, 12.0; mol wt (mass spectrometrically) 554.

Filtrate F was treated with *S*-benzylthiuronium chloride (1.22 g, 6 mmol) in H_2O (20 mL); the precipitate (mp 243–245 °C, yield 64%) was ***S*-benzylthiuronium diisophor-2(7)-ene-1-sulfonate (10)**: mp 245–247 °C (from 50% aqueous MeOH); IR 3320–3220 s mult, 3110 vs br (NH), 2940–2860 vs, 1460 ms, 1435 m (CH_3, CH_2), 1390, 1365 mw (CMe_2), 1195 vs, 1165 vs, 1055 vs (SO_2OH), 775 mw, 705 mw (Ph) cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_3S{\cdot}C_8H_{10}N_2S$: C, 63.4; H, 8.1; N, 5.7; S, 13.0. Found: C, 64.0; H, 8.8; N, 5.6; S, 13.5.

Tetracyclic Condensation Products. 3,21-Dehydro-1-*S*-isothioureidodiisophora-2,7-dien-3-ol (16; (2,3,4,5,6,8,9,10,-11,11a-Decahydro-2-imino-5,5,8,10,10-pentamethyl-8,11a-methanocycloocta[*d*,*e*][3,1]benzothiazine)). (a) A solution of **13** (13.8 g, 50 mmol) and thiourea (4.18 g, 55 mmol) in CF_3CO_2H (60 mL) was boiled under reflux for 20 h, distilled to one-third volume, and stirred into ice–water. The precipitated resin, rinsed with H_2O, was dissolved in MeOH (40 mL) with the least possible warming. The deposited prisms (65–72%) gave pale yellow solvated **16** trifluoroacetate: mp 181–183 °C (from MeOH); IR 3430 ms (NH_3^+), 2970–2870 vs, 1470 ms, 1440 ms (CH_3, CH_2), 1675 vs, 1640 vs br (? C=N, NH), 1390 ms, 1365 s (CMe_2), 1200 vs, 1180 vs, 1135 vs (CF_3COOH) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2S{\cdot}CF_3COOH{\cdot}CH_3OH$: C, 57.1; H, 7.1; N, 6.1; S, 6.9. Found: C, 57.2; H, 7.4; N, 5.9; S, 9.0.

(b) Base. The trifluoroacetate (9.25 g, 20 mmol) in hot EtOH (50 mL), treated with 3 M NaOH (16.7 mL, 50 mmol) gave felted needles on cooling (95%), which afforded pale yellow **16**, mp 186–188 °C (from MeOH, 5 mL/g, recovery low); UV λ_{max} 214 nm (log ϵ 3.85), 237 (4.01), 328 (3.90). IR 3450 ms (? NH_2), 3390 m, 3290 ms, 3020 m (NH), 2950–2870 vs, 1460 m, 1435 mw (CH_3, CH_2), 1635–1625 s d br, 1600 ms (? C=N, NH), 1555, 1545 vs d (? NH), 1385 ms, 1365 ms (CMe_2), 1330 m br, 1240 m, 1175 mw, 1040 mw, 975 mw, 935 mw cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2S$: C, 72.15; H, 8.9; N, 8.9; S, 10.1. Found: C, 72.1;, H, 8.9; N, 8.8; S, 10.0.

Interaction of **12** and thiourea in boiling 100% HCO_2H (6 h) and immediate conversion of the crude resin into the base as above gave **16** (yield, 70%), identical with the foregoing material.

Stability toward Alkali. The base **16** (2 mmol) was recovered (85%) after being refluxed in EtOH (12 mL)–MeOH (12 mL)–5 M aqueous NaOH (6 mL) for 2 h.

(c) The picrate of **16** had mp 224–227 °C dec (from EtOH). Anal. Calcd for $C_{19}H_{28}N_2S{\cdot}C_6H_3N_3O_7$: C, 55.05; H, 5.7; N, 12.8; S, 5.9. Found: C, 54.6; H, 5.8; N, 12.4; S, 5.7.

(d) Hydrochloride. A solution of **12** (2.95 g, 10 mmol) and thiourea (0.84 g, 11 mmol) in EtOH (25 mL) was refluxed for 16 h and then distilled to small bulk. The solid (38%) gave pale yellow **16** hydrochloride: mp 273–275 °C dec (from 70% ethanol); IR 3430 mw, 3160 s (NH, ? amide), 2960–2880 vs, 1475 ms, 1455 ms (CH_3, CH_2), 2730 s (NH_2^+), 1655 ms, 1630 vs, 1585 vs (C=N, NH, C=C conjugated), 1390 ms, 1365 ms (CMe_2) cm^{-1}. Except for the absence of the multiple peak at 1200–1135 cm^{-1}, this spectrum closely resembles that of the trifluoroacetate. Anal. Calcd for $C_{19}H_{28}N_2S{\cdot}HCl$: C, 64.7; H, 8.2; N, 7.9; S, 9.1; Cl, 10.1. Found: C, 64.7; H, 8.0; N, 8.0; S, 9.1; Cl, 10.4. Another 12–15% of **16** was isolable as the picrate from the filtrates.

(e) Use of 1-carboxydiisophor-2(7)-en-3-one[19,32] in procedure a resulted in the recovery (70%) of the starting material.

Benzoyl Derivative of 16. A solution of **16** (0.79 g, 2.5 mmol) in pyridine (10 mL) was treated with benzoyl chloride (0.42 g, 3 mmol), kept at 100 °C for 2 h, then added to ice–water, and acidified with HCl. The precipitate gave the solvated derivative: mp 192–194 °C (from EtOH, yield 72%); UV λ_{max} 211 nm (log ϵ 4.00), 244 (4.13), 362 (4.01); IR 3140 m, 3000 m (NH), 2950–2850 vs, 1445–1430 vs br (CH_3, CH_2), 1640 vs (CO of COPh), 1565, 1555, 1535 vs br (C=N, NH, C=C conjugated), 1390 ms, 1380 s (CMe_2) 730 s, 715 s (Ph), 1355 vs, 1260, 1250 vs d cm^{-1}. Anal. Calcd for $C_{26}H_{32}N_2OS{\cdot}C_2H_5OH$: C, 72.1; H, 8.15; N, 6.0; S, 6.9. Found: C, 72.3; H, 7.5; N, 6.3; S, 6.9. Desolvation occurred at 110 °C (2 mm) (6 h) without change in appearance. Anal. Calcd for $C_{26}H_{32}N_2OS$: C, 74.3; H, 7.6; N, 6.7. Found: C, 74.2; H, 7.6; N, 6.7.

3,21-Dehydro-1-*S*-isothioureido-5,11-bisnordiisophora-2,7-dien-3-ol, prepared as **16** from the 5,11-bisnor homologue[31] of **12**, but by direct conversion of the resinous trifluoroacetate into the base, formed pale yellow prisms: mp 193–196 °C (from EtOH; overall yield, 40%); UV λ_{max} 214 nm (log ϵ 3.89), 238 (4.03), 330 (3.90); IR 3430 s (? NH_2), 3260 s, 3070 s (NH), 2940–2860 vs, 1460 s, 1430 m (CH_3, CH_2), 1635 vs, 1590 s (C=N, NH, C=C conjugated), 1555 vs (? NH) cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2S$: C, 70.8; H, 8.3; N, 9.7; S, 11.1. Found: C, 70.7; H, 8.4; N, 9.6; S, 11.2. Its **picrate** had mp 181–184 °C (from EtOH). Anal. Calcd for $C_{17}H_{24}N_2S{\cdot}C_6H_3N_3O_7$: C, 53.4; H, 5.2; N, 13.5. Found: C, 53.1; H, 5.2; N, 13.1.

Use of Substituted Thioureas. 3,21-Dehydro-1-(*N*-phenyl-*S*-isothioureido)diisophora-2,7-dien-3-ol (17). **(a.1)** A solution of **12** (7.35 g, 25 mmol) and phenylthiourea (4.18 g, 27.5 mmol) in CF_3CO_2H (50 mL) was refluxed for 24 h, distilled to half-bulk, and stirred into ice–water (60 mL). The precipitated resin solidified on being ground with H_2O and afforded pale yellow **17** trifluoroacetate: mp 168–169 °C (from EtOH; yield, 48–55%); IR 2950, 2910–2850 vs, 1455 ms, 1435 s (CH_3, CH_2), 2700 vs (NH_2^+), 1670 vs–1615 s mult (C=N, NH, C=C conjugated), 1380 s, 1365 ms sh (CMe_2), 1205, 1185, 1130 vs mult (CF_3COOH), 765 ms, 725 vs (Ph), 1590 vs cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2S{\cdot}CF_3COOH$: C, 64.0; H, 6.5; N, 5.5; S, 6.3; F, 11.3. Found: C, 63.9; H, 6.7; N, 5.5; S, 6.8; F, 12.3. More product (up to 25%) was isolable from the filtrates as the picrate (see below).

(a.2) The 1-hydroxy analogue **13** or the 1-ethoxy analogue **14** of **12** functioned as equally suitable starting materials in this reaction, producing comparable yields.

(b.1) Treatment of a solution of the trifluoroacetate (2.53 g, 5 mmol) in hot EtOH (30 mL) with 3 M NaOH (8.3 mL, 25 mmol) and dilution with H_2O precipitated a pale yellow solid (mp 225–228

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Table II. Tetracyclic Condensation Products: 8,11a-Methanocycloocta[*d*,*e*][3,1]benzothiazines

compd	method[k] (reflux time, h)	mp, °C (yield, %)	mol form.	analysis	calcd	found	UV λ, nm (log ε)	IR ν, cm^{-1}
18·TFA[a]	A (24)	125–127[b] (56)	$C_{26}H_{34}N_2S$·CF_3COOH	C	64.6	64.1		3500–3400 s mult (NH), 2950–2830 vs br 1470, 1460 mw (CH_3, CH_2), 2730 ms br (NH_2^+) 1675 vs, 1650 vs br (C=N, NH, C=C conjugated), 1395 s, 1385 vs (CMe_2), 1200, 1180 vs, 1135 vs (CF_3COOH), 830 ms (para substituted Ar)
				H	6.7	7.3		
				N	5.4	6.6		
				S	6.5	7.0		
18	B	206–208[c] (92)	$C_{26}H_{34}N_2S$	C	76.85	77.6	215 (4.15)	3420 ms d, 3180 ms, 3100 ms (NH), 2940–2850 vs, 1470, 1460 ms (CH_3, CH_2), 1600–1580 vs br (C=N, NH, C=C conjugated), 1385, 1365 s (CMe_2), 835 s (para substituted Ar)
				H	8.4	8.5	254 (3.93)	
				N	6.9	6.5	340 (4.14)	
				S	7.9	7.8		
19·TFA[a]	A (24)	146–148[b] (65)	$C_{25}H_{31}ClN_2S$·CF_3COOH	C	59.95	60.1		3450 ms br (? NH), 2960, 2910 vs d–2850 vs, 1475, 1465 m (CH_3, CH_2), 2700–2640 s (NH_2^+) 1675 vs, 1620 s br (C=N, NH, C=C conjugated), 1395 ms, 1385 s (CMe_2), 1200–1175 vs, 1140 vs (CF_3COOH), 835 s (para substituted Ar), 725 s (Cl)
				H	5.9	5.8		
				N	5.2	5.8		
19	B	219–221[c] (85)	$C_{25}H_{31}ClN_2S$	C	70.3	69.6	215 (4.10)	3440 ms, 3200 ms, 3120 ms (NH), 2960, 2920 vs sh d–2850 vs, 1470, 1460 ms (CH_3, CH_2), 1610, 1585 vs (C=N, NH, C=C conjugated), 1380 ms (CMe_2), 845 s (para-substituted Ar), 725 mw (Cl), 1220, 1210 vs d
				H	7.3	7.1	262 (3.93)	
				N	6.6	6.7	343 (4.16)	
				Cl	8.3	8.3		
20	C[d]	206–208[e] (48)	$C_{31}H_{36}N_2S$	C	79.5	79.4	222 (4.22)	2940, 2910 vs d–2860 vs, 1470, 1460 m (CH_3, CH_2), 1605 vs, 1570 vs br (C=N, C=C conjugated), 1395 m, 1385 ms (CMe_2), 775 ms, 765 vs, 725 ms, 695 vs (2 Ph), 1500 s, 1360 vs, 1290 vs, 1215 s, numerous unassigned peaks (ms) between 1200 and 800
				H	7.7	7.9	310 (4.15)	
				N	6.0	5.6		
				S	6.8	7.0		
21	C[d] (6)	167–169[e] (32)	$C_{31}H_{36}N_2S$	C	79.5	79.4	217 (4.23)	2960, 2910 vs d–2860 vs, 1460 m (CH_3, CH_2), 1590 ms, 1550 vs sh, 1540 vs (C=N, C=C conjugated), 1385, 1370 mw (CMe_2), 755 s, 705 m, 695 vs (2 Ph), 1500 vs, 1270 vs
				H	7.7	7.6	290 (3.96)	
				N	6.0	6.2	356 (4.08)	
				S	6.8	7.2		
22[f]	C (6)	119–120[c] (38)	$C_{27}H_{36}N_2S$	C	77.1	77.2	211 (4.16)	2950–2850 vs, 1475 m, 1465 ms (CH_3, CH_2), 1555 vs (C=N, C=C conjugated), 1395 ms, 1385 s (CMe_2), 770 m, 695 s (Ph)
				H	8.6	8.8	342 (4.03)	
				N	6.7	6.45		
				S	7.6	7.8		
23·2TFA	A (6)	94–97[g] (43)	$C_{21}H_{32}N_2S$·$2CF_3COOH$	C	52.4	52.2		2940–2880 vs, 1465 ms (CH_3, CH_2), 1605 vs (C=N, C=C conjugated), 1385, 1370 ms (CMe_2), 1200–1145 vs mult (CF_3COOH)
				H	5.9	5.9		
				N	4.9	4.8		
				S	5.6	5.9		
23[h]	B	106–108[i] (48)	$C_{21}H_{32}N_2S$	C	73.25	72.9	218 (3.92)[j]	2960–2870 vs, 1475 ms (CH_3, CH_2), 2820 s sh (NMe), 1590 ms sh, 1565–1555 vs d (C=N, C=C conjugated), 1385 ms, 1380 s (CMe_2), 1355 vs
				H	9.3	9.2	244 (3.97)	
				N	8.1	8.2	337 (4.03)	
				S	9.3	9.2		

[a] TFA = Trifluoroacetate. [b] Crystallized from ethanol–water. [c] Crystallized from ethanol. [d] Up to 35% of the substituted thiourea employed was recovered unchanged as the initial crop. [e] Crystallized from 2-ethoxyethanol. [f] The picrate of **22** had mp 191–192 °C (from ethanol). Anal. satisfactory. [g] Crystallized from light petroleum. [h] The picrate of **23** had mp 165–168 °C (from ethanol). Anal. satisfactory. [i] Crystallized from methanol. [j] Plateau. [k] A: prepared as **17**, procedure a. B: prepared as **17**, procedure b. C: prepared as **17**, combination of procedures a and b, without isolation of the trifluoroacetate.

°C, yield 95%), which gave **17**: mp 235–237 °C (from 2-ethoxyethanol); UV λ_{max} 212 nm (log ε 4.25), 258 (4.03), 340 (4.19); IR 3420 ms, 3180 ms, 3100 ms (NH), 2950–2900 vs, 1475, 1455 ms (CH_3, CH_2), 1615–1590 vs (C=N, NH, C=C conjugated), 1385, 1365 s (CMe_2), 775 s, 700 s (Ph), 1655 mw, 1340 ms, 1310 s, 1220, 1210 s d br, 865 mw cm^{-1}, and numerous unassigned peaks (mw) between 1200 and 900 cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2S$: C, 76.5; H, 8.2; N, 7.1; S, 8.2; mol wt 392. Found: C, 76.2; H, 8.05; N, 7.2; S, 8.3; mol wt (mass spectrometrically) 392.

(**b.2**) The use of formic or acetic acid (50 mL) as reaction medium (procedure a, reflux 6 h) and immediate conversion of the crude resinous salts into the base (procedure b) gave **17** in 60% and 25% yields, respectively (from **12**). The reactant **12** was recovered (up to 90%) when the condensation was attempted in boiling EtOH (8 or 72 h).

(**c**) The **picrate** of **17** had mp 196–198 °C (from EtOH–acetone, 3:1). Anal. Calcd for $C_{25}H_{32}N_2S{\cdot}C_6H_3N_3O_7$: C, 59.9; H, 5.6; N, 11.3; S, 5.15. Found: C, 60.1; H, 5.8; N, 11.1; S, 5.3.

(**d**) **Stability of 17.** The base was recovered (82%) after its solution in boiling 2-ethoxyethanol was treated dropwise with 3 M NaOH (6 mol) and refluxed for 4 h. The action of alkaline sodium plumbite in the presence of EtOH (to facilitate dissolution of **17**) did not give lead sulfide.

(**e**) The **benzoyl derivative** of **17** (prepared as that of **16**) formed pale yellow prisms: mp 188–190 °C (yield 80%); UV λ_{max} 211 nm (log ε 4.18), 239 (4.19), 353 (3.80); IR 2950, 2910–2850 vs, 1490 m, 1450 m (CH_3, CH_2), 1685 vs (C=O of Bz, ? C=N), 1385 mw, 1360 m (CMe_2), 1250 vs, 1240 s t, 1205 vs (C–O ester), 785 m, 760 ms, 725 m, 700 vs (2 Ph) cm^{-1}. Anal. Calcd for $C_{32}H_{36}N_2OS$: C, 77.4; H, 7.3; N, 5.6. Found: C, 77.1; H, 7.3; N, 5.55.

Data concerning analogous 8,11a-methanocycloocta[*d*,*e*][3,1]-benzothiazines **18–23**, prepared by the procedures detailed for **17**, are summarized in Table II.

Use of *N*,*N*,*N*′-Trisubstituted Thioureas. The interaction of **12** or **13** and *N*,*N*,*N*′-trimethyl- or *N*,*N*-dimethyl-*N*′-*p*-tolyl-

thiourea under the usual conditions gave only 1-(trifluoroacetoxy)diisophor-2(7)-en-3-one (ca. 50%), indentical with authentic material (see below).

1-(Trifluoroacetoxy)diisophor-2(7)-en-3-one (26). A solution of **12** (0.89 g, 3 mmol) in CF_3CO_2H (10 mL) was refluxed for 6 h and then added to ice–water. The resinous precipitate solidified on being stirred with H_2O and gave **26**: mp 107–108 °C (from light petroleum; yield, 65%); IR 2950 s–2870 ms, 1455 m mult (CH_3, CH_2), 1765 vs (CO of $COCF_3$), 1660 vs (CO, ring), 1630 ms (C=C conjugated), 1395 vs sh, 1385 vs (CMe_2), 1220, 1210 vs (CF_3), 1175, 1160 vs (C–O ester). Anal. Calcd for $C_{20}H_{27}F_3O_3$: C, 64.5; H, 7.3; F, 15.3. Found: C, 64.75; H, 7.5; F, 15.15.

Use of Thioamides. 3,21-Dehydro-1-*S*-isothioacetamidodiisophora-2,7-dien-3-ol (24) and Phenyl Analogue 25. A solution of **12** (1.47 g, 5 mmol) and thioacetamide (0.41 g, 5.5 mmol) in CF_3CO_2H (10 mL) was refluxed for 6 h, the crimson liquid stirred into H_2O, and the precipitated resin treated in EtOH with picric acid (1.15 g, 5 mmol). The **24** picrate had mp 169–172 °C dec (from EtOH; yield, 72%). Anal. Calcd for $C_{20}H_{29}NS \cdot C_6H_3N_3O_7$: C, 57.3; H, 5.9; N, 10.3; S, 5.9. Found: C, 57.5; H, 6.8; N, 10.1; S, 5.9.

The use of thiobenzamide (0.75 g, 5.5 mmol) similarly gave orange **25** picrate: mp 157–159 °C (from EtOH; yield, 85%). Anal. Calcd for $C_{25}H_{31}NS \cdot C_6H_3N_3O_7$: C, 61.4; H, 5.6; N, 9.2; S, 5.3. Found: C, 61.4; H, 5.7; N, 9.2; S, 5.5.

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A New, Asymmetric Synthesis of Lipids and Phospholipids

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Titanium-assisted nucleophilic opening of (*S*)-glycidol (**2**) with stearic acid gives (*S*)-(+)-1-stearoyl-*sn*-glycerol (**3**). Silylation of **3** with *tert*-butyldimethylchlorosilane can be done to selectively form (*R*)-(+)-1-stearoyl-3-(*tert*-butyldimethylsilyl)-*sn*-glycerol (**4**). Esterification of **4** with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride gives a "Mosher ester" (**5**) whose high-field NMR spectrum is suitable for determination of enantiomeric excess. Esterification of **4** with stearoyl chloride followed by removal of the silyl protecting group gives the diacylglyceride, (*S*)-(−)-1,2-distearoyl-*sn*-glycerol (**7**). The silyl group may be removed without acyl migration by the use of *N*-bromosuccinimide/DMSO/THF/H_2O for the hydrolysis. Literature methods may be used to complete the assembly of the phosphorylcholine head group. This short synthetic route offers a new entry to the synthesis of optically active phospholipids and mono-, di-, and triacylglycerides.

Introduction

At the crux of phospholipid chemistry is the need to generate and maintain the optical activity of a derivatized glycerol molecule. The first synthetic solution to this problem was devised by Baer and co-workers.[1] Beginning in 1937 with the preparation of (*S*)-2,3-*O*-isopropylideneglycerol from D-mannitol[2] and culminating in 1950 with the synthesis of 1,2-distearoyl-*sn*-glycero-3-phosphorylcholine,[3] Baer developed a convenient synthetic route to optically active phospholipids. The route from D-mannitol to phospholipids in which the two acyl groups are identical requires nine synthetic steps, while synthesis of phospholipids in which the two acyl groups are different requires fourteen steps. Although improvements have been made in individual steps and other chiral precursors, such as serine,[4] have been used, the synthetic scheme devised by Baer remains the basis for much of the phospholipid chemistry performed today.[5]

A second synthetic approach to phospholipids is, in reality, only semisynthetic in nature. This method uses phospholipids isolated from natural sources as substrates for enzymic cleavage, i.e., with PLA_1, PLA_2, etc., of a single substituent followed by chemical resynthesis of an analogous phospholipid.[6] This approach finds greater application in cases where small quantities of phospholipid analogs are needed.

Several recent advances in asymmetric epoxidation chemistry seemed to us to offer the possibility of a new synthetic route to optically active lipids and phospholipids. The asymmetric epoxidation of allylic alcohols, introduced by Katsuki and Sharpless in 1980,[7] is a powerful method for the introduction of chirality into organic molecules. When the simplest allylic alcohol, allyl alcohol, is used in this reaction, the product is optically active glycidol.[8] Glycidol[9] may be envisioned as a derivative of glycerol and occasionally has been used as an intermediate in lipid chemistry. Optically active glycidol has been used to prepare optically active triglycerides,[4] while racemic glycidol has been used for the synthesis of a dithio ester analogue of a phosphatidylcholine[10] and the synthesis of monoacylglycerols.[11]

Until recently, the preparation of optically active glycidol by asymmetric epoxidation of allyl alcohol was somewhat impractical because of the difficulty with which the product was isolated. Both the solubility of the product in the reaction quench and the reactivity of glycidol con-

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