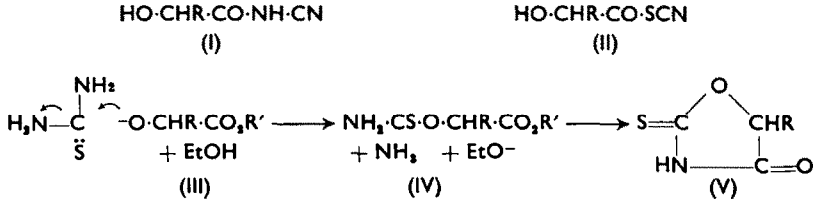
Tetrahedron, 1958, Vol. 3, pp. 310–316. Pergamon Press Ltd., London

NOTES

Acyl thiocyanates: on the nature of Clemmensen and Heitman's "Glycollyl and lactyl thiocyanates"

(*Received* 16 *October* 1957)

CLEMMENSEN and Heitman[1] found that interaction of ethyl glycollate or lactate with thiourea in refluxing ethanolic sodium ethoxide afforded, in addition to the expected acyl cyanamides (I; R = H and Me), small amounts of byproducts, which they concluded were acyl thiocyanates (II; R = H and Me). From our experience with acyl *iso*thiocyanates,[2] we suspected that the proposed structures were erroneous. Repetition of Clemmensen and Heitman's experiments revealed that ammonia was liberated, and we therefore inferred that the side-reactions comprised nucleophilic attack by the ethoxycarbonylalkoxide ions (III; R = H and Me, R′ = Et) on the carbon atom of thiourea followed by cyclisation of the intermediate *O*-thiocarbamoyl-glycollic or -lactic esters (IV; R = H and Me, R′ = Et) to the 2-thioöxazolid-4-ones (V; R = H and Me). Ahlqvist[3] found that the acid (IV; R = R′ = H) cyclised similarly on prolonged heating. Our thesis was confirmed, since the byproducts which we isolated had melting points which corresponded to those quoted by Clemmensen and Heitman, and were identical with authentic samples of the 2-thioöxazolid-4-ones.[4]



So far as we are aware, diphenylcarbamoyl thiocyanate[5] is the only acyl thiocyanate whose structure has been adequately established. It is possible that it owes its existence to the steric retardation of thermal isomerisation to the acyl *iso*thiocyanate, which is generally the more stable structure. It is noteworthy that the infra-red spectrum of diphenylcarbamoyl thiocyanate has a weak, sharp band at 2161 cm^{-1} similar to the spectra of alkyl thiocyanates and differing from the intense, broad bands in the spectra of alkyl *iso*thiocyanates and benzoyl *iso*thiocyanate.[6]

EXPERIMENTAL

2-Thioöxazolid-4-one. A mixture of ethyl glycollate (10·4 g) and thiourea (9 g) in a solution of sodium (2 g) in ethanol (100 cm^3) was heated under reflux for 2 hr. The solution was evaporated, diluted with water (100 cm^3), brought to pH 5 with acetic acid, and continuously extracted overnight with ether. The extract was evaporated, and the residue was purified by counter-current distribution between ether and water. The product (0·41g) was located by paper chromatography in butan-1-ol saturated with water (R_F 0·56), and isolated by evaporation. Recrystallised from water, it had m.p.

[1] E. Clemmensen and A. H. C. Heitman, *Amer. Chem. J.* 42, 319 (1909).
[2] D. T. Elmore, J. R. Ogle, W. Fletcher and P. A. Toseland, *J. Chem. Soc.* 4458 (1956); D. T. Elmore and J. R. Ogle, *Proc. Chem. Soc.* 289 (1957); *J. Chem. Soc.* 1141 (1958).
[3] A. Ahlqvist, *J. Prakt. Chem.* 99, 45 (1919).
[4] J. S. H. Davies, W. H. Hook and F. Long, *J. Chem. Soc.* 36 (1950).
[5] T. B. Johnson and L. H. Levy, *Amer. Chem. J.* 38, 456 (1907).
[6] D. T. Elmore, Unpublished results.

110–111° and in admixture with an authentic sample;[4] the two specimens had identical infra-red spectra.

5-Methyl-2-thioöxazolid-4-one. The reaction was carried out exactly as described by Clemmensen and Heitman.[1] After removal of lactyl cyanamide, the mother-liquors were continuously extracted overnight with ether. The extract was evaporated and the residue was extracted with benzene-ether. The resultant extract was filtered and evaporated, and the residue (1·86 g) crystallised at 0°. Recrystallised twice from benzene-light petroleum (b.p. 40–60°) and twice from water, it had m.p. 91·0–91·5° and in admixture with an authentic specimen.[4] Comparison of infra-red spectra confirmed their identity.

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The rearrangement of scopinone to *m*-hydroxybenzaldehyde

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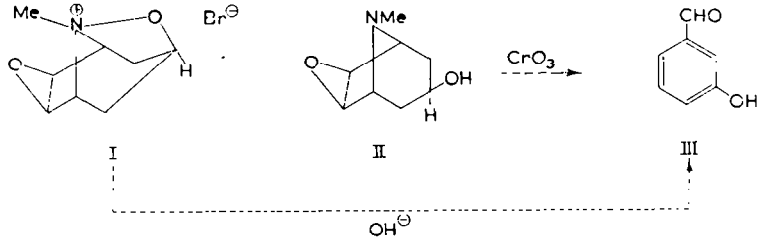
RECENT studies of the elimination reactions of a variety of tropinone derivatives have shown that these reactions usually follow a normal course, giving rise to the expected troponoid products.[1] In this context, the early reports by Polonovski and Polonovski that the base degradation of scopinium bromide (I) and that chromic acid oxidation of *pseudo*scopine (II) both give a rearranged product, *m*-hydroxybenzaldehyde (III),[2] were of special interest. In order to gain further insight into these



transformations, a study of the elimination reactions of scopinone (IV) and its methobromide (V) has been carried out.

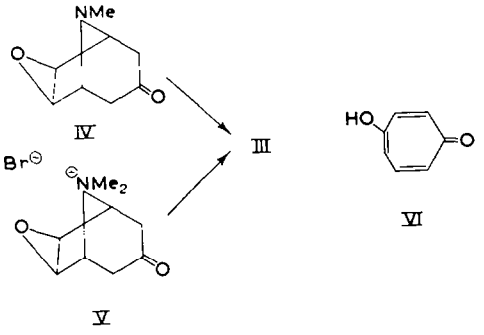
Scopinone was prepared for the first time by Heusner, as described in the adjoining Communication.[3] Scopinone methobromide (V) was found to suffer rapid degradation when treated with one equivalent of sodium bicarbonate at steam-bath temperatures. The chief organic product, formed in ca. 80 per cent yield, was found to be *m*-hydroxybenzaldehyde, identified both by spectral means and by isolation and comparison with an authentic sample of (III). Even in the absence of external base, (V) is converted into (III) after a short induction period. In this case it appears that the elimination is catalysed by the dimethylamine, which increases in concentration as the reaction progresses. Somewhat surprisingly, scopinone itself was found to undergo an analogous rearrangement, with or without added base, and even in the presence of acid. Thus, both elimination and rearrangement proceed with unprecedented ease in this series.

[1] J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, *J. Amer. Chem. Soc.* **77**, 4401 (1955); J. Meinwald and O. L. Chapman, *J. Amer. Chem. Soc.* **78**, 4816 (1956); E. E. van Tamelen, P. Barth and F. Lornitzo, *J. Amer. Chem. Soc.* **78**, 5442 (1956); J. Meinwald and O. L. Chapman, *J. Amer. Chem. Soc.* **80**, (1958).

[2] For leading references to these papers, see R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. I, pp. 302–307. Academic Press, New York (1950).

[3] A. Heusner and K. Zeile, *Tetrahedron* **3**, 313 (1958).

The possibility that (IV) or (V) are first converted to γ-tropolone (VI), which might then rearrange to (III) via a process consisting of a reverse aldol condensation followed by cyclization in a new



sense, has been excluded by an experiment in which (VI) was shown to be completely stable to prolonged base treatment.* We hope to publish a more detailed account of this work, as well as a discussion of its mechanistic implications, in the *Journal of the American Chemical Society*.

Acknowledgements—We are thankful to Dr. Alex Heusner for communicating his results before publication, as well as for providing a generous sample of scopinone methobromide. The partial support of this research by a Frederick Gardner Cottrell grant from the Research Corporation, New York, is gratefully acknowledged.

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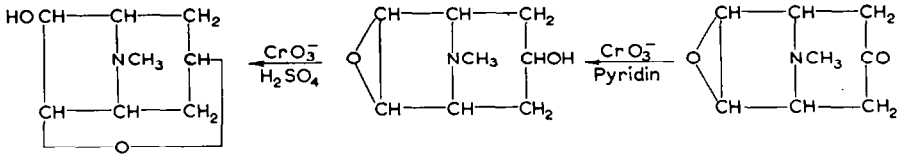
* A preliminary indication of the stability of γ-tropolone to base had already been provided by the work of T. Nozoe *et al.*[4]

[4] T. Nozoe, T. Mukai, Y. Ikegama and Toda, *Chem. & Ind.* 66 (1955).

Partialsynthese von Scopinon

(*Received* 17 *January* 1958)

IM Pyrrolidinring substituierte Derivate des Tropinons sind in letzter Zeit mehrfach als Ausgangsmaterialien für die Darstellung von Tropon und seinen Derivaten verwandt worden.[1] In diesem Zusammenhang teilen wir die Partialsynthese des bisher noch nicht bekannten Scopinons (6,7-Oxido-tropinon; III) mit. Versuche zur Totalsynthese von III hatten zu einer Ausweichreaktion



I III

[1] J. Meinwald und O. L. Chapman, *J. Amer. Chem. Soc.* **78**, 4816 (1956), *Ibid.* **80**, 633 (1958); E. E. van Tamelen, B. Barth und F. Lornitzo, *Ibid.* **78**, 5442 (1956).

geführt,[2] während die Einwirkung von Chromtrioxyd in schwefelsaurer Lösung auf den entsprechenden Alkohol Scopin (II) lediglich Isomerisierung zu Scopolin (I) ergab.[3]

Wie wir fanden, lässt sich indessen II[3,4] durch das Chromtrioxyd-Pyridin-Reagens von Sarett und Mitarbeitern[5] mit Ausbeuten um 25% zu III oxydieren [Schmp. 65–67°, im I.R.-Spektrum ausgeprägte Carbonylbande bei 5·87 μ und zwei Oxiranbanden bei 11·62 und 11·88 μ, Pikrat Schmp. 175° (Zers.), Methobromid Schmp. 176° (Zers.)].

Über den Hofmannschen Abbau von III-Methobromid berichten Meinwald und Chapman in der nachstehenden Mitteilung.[6] Die ausführliche Beschreibung unserer Versuche wird in den *Chemischen Berichten* erfolgen.

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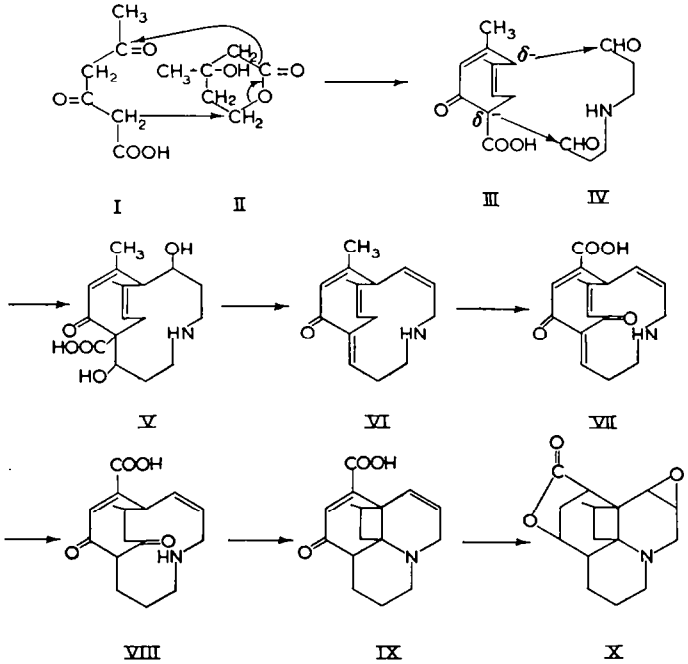
[2] Cl. Schöpf und A. Schmetterling, *Z. Angew. Chem.* **64**, 591 (1952); J. C. Sheehan und B. M. Bloom, *J. Amer. Chem. Soc.* **74**, 3825 (1952).
[3] R. Willstätter und E. Berner, *Ber. Dtsch. Chem. Ges.* **56**, 1079 (1923).
[4] J. Meinwald und O. L. Chapman, *J. Amer. Chem. Soc.* **79**, 605 (1957).
[5] G. I. Poos, G. E. Arth, R. E. Beyler und L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[6] J. Meinwald und O. L. Chapman, *Tetrahedron* **3**, 311 (1958).

The biogenesis of annotinine

(*Received* 28 *February* 1958)

Recently, the structure of annotinine (X) proposed by Wiesner *et al.*[1] has been confirmed by a striking three-dimensional analysis of annotinine bromohydrin.[2] The following biogenetic scheme is proposed for this interesting molecule.



[1] K. Wiesner, W. A. Ayer, L. R. Fowler and Z. Valenta, *Chem. & Ind.* 564 (1957).
[2] M. Przybylska and L. Marion, *Canad. J. Chem.* **35**, 1075 (1957).

Initial condensation is postulated between β,δ-diketocaproic acid (I) [derived from three acetate units] and mevalonic lactone (II) [a key intermediate in cholesterol[3] and terpene[4,5,6] biosynthesis], decarboxylation and dehydration leading to (III). Nitrogen is introduced into the molecule by the condensation of (III) with the dialdehyde amine (IV). This amine, or its biological equivalent, can be derived from two molecules of aspartic acid by conventional metabolic steps. It is of interest to note that Robinson[8] has proposed that the higher homologue of (IV) is a precursor of the pyrrolizidine alkaloids. Decarboxylation and dehydration of (V) yields compound (VI), which is oxidized at the allylic carbons to give (VII). Partial reduction results in the formation of (VIII), which undergoes an intramolecular Mannich reaction to give (IX), which contains the *cyclo*butane ring. Final steps are uneventful, involving reduction of the α,β-unsaturated ketone, lactonization and epoxidation of the double bond.

It is our intention to test this hypothesis by using radioactive tracers.

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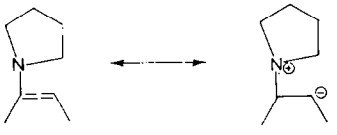
[3] P. A. Tavormina, M. H. Gibbs and J. W. Huff, *J. Amer. Chem. Soc.* **78**, 4498 (1956).
[4] A. J. Birch, R. J. English, R. A. Massey-Westropp and H. Smith, *J. Chem. Soc.* 369 (1958).
[5] G. D. Braithwaite and T. W. Goodwin, *Biochem. J.* **67**, 13P (1957).
[7] E. C. Grob, *Chimia* **11**, 338 (1957).
[8] R. Robinson, *The Structural Relations of Natural Products* p. 72. Clarendon Press, Oxford (1955).

The alkylation of pyrrolidine enamines

(*Received* 20 *February* 1958)

THE elegant use of pyrrolidine enamines (I, Ia) of ketones as active intermediates for their C-alkylation and C-acylation has been described by Stork *et al.*,[1] the form (Ia) being that involved in reaction:



I Ia

It was observed that monosubstitution only occurred (cf. Stork and Landesman[2]), for example, with *cyclo*hexanone and 5-phthalimido-2-tetralonepyrrolidine enamines, and the enamine of 2-methyl-*cyclo*hexanone was not C-methylated with methyl iodide.

That this monosubstitution may be a combination of steric effects due to the presence of the pyrrolidine ring and the α-alkyl substitution, which in the cases of the α-methylated *cyclo*hexanone (II) and 5-phthalimido-2-tetralone (III)-pyrrolidine enamines prevents the entry of a second methyl can be seen from measurements on Barton models[3] of (II) and (III, R = phthalimido). These give values of ca. 1 and 1·4 Å, respectively, for the distances between the α-hydrogen atoms of the pyrrolidine ring and the nearest hydrogen atoms of the α-methyl groups when these are equatorial. These are comparable to the "interference radii" of two hydrogen atoms (1·5 Å) of Crombie.[4] Hence the methyl groups must take up the axial conformation in the active forms (II) and (III) so that equatorial substitution is blocked by the pyrrolidine ring, and in the case of (II) axial substitution in the 6-position is also blocked by the axial methyl group. Were the α-methyl groups to remain equatorial in (II) and (III), the coplanarity of the four bonds from the $C{=}\overset{\oplus}{N}$ group [a necessary condition[5] for the existence of the forms (II) and (III)] would be prevented, and hence C-alkylation again inhibited. In

[1] G. Stork, R. Terrell and J. Szmuszkovicz, *J. Amer. Chem. Soc.* **76**, 2029 (1954).
[2] G. Stork and M. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5128 (1956).
[3] D. H. R. Barton, *Chem. & Ind.* 1136 (1956).
[4] Cf. E. A. Braude and F. Sondheimer, *J. Chem. Soc.* 3754 (1955).
[5] M. J. S. Dewar, *Electronic Theory of Organic Chemistry* Chap. I. Oxford University Press (1948).