[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Structure of the Anhydrobromonitrocamphanes

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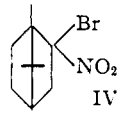
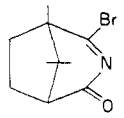
Structures I and II are proposed for anhydrobromonitrocamphane-I and -II, first prepared in 1899 by acid treatment of 2-bromo-2-nitrocamphane.[2]

During the course of his investigations dealing with the preparation and properties of (−)-2-bromo-2-nitrocamphane (IV), Forster[2] subjected

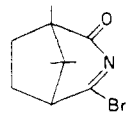


IV

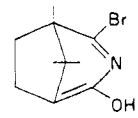
the substance to the action of concentrated sulfuric acid at 0° and found that there was formed, in addition to some 2-bromo-*p*-cymene, a crystalline *monodehydration product* (I). The same author noted further that hot, aqueous mineral acid induced the transformation of this anhydride into a well-defined *isomer* (II).[2] A similar pair of products was secured from 2-chloro-2-nitrocamphane,[3] although 2-nitro- and 3-bromo-2-nitrocamphane were indifferent to the acid reagent.[4] Following additional study,[4] Forster in 1901 suggested for I (referred to herein as "anhydrobromonitrocamphane-I") an *N-acyliminobromide structure* (V or VI), which Ginnings and Noyes[5] later adopted in



V



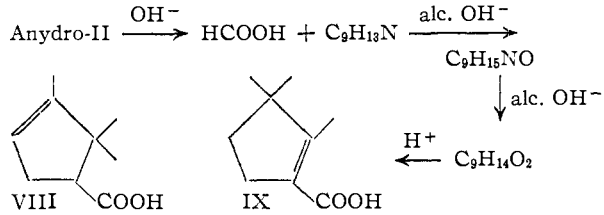
VI



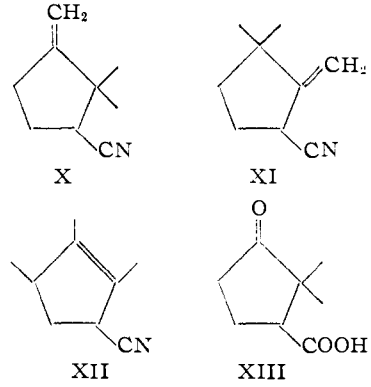
VII

their *enol formulation* (VII) for the isomer II ("anhydrobromonitrocamphane-II"). For several, readily apparent, reasons the proposal VII can be dismissed. Moreover, Forster's structure hardly accords with the experimental facts; for example, mineral acid treatment of a compound possessing structure V or VI should give camphoric acid or camphorimide. The ineptness of the bromonitrocamphane structure for accommodating a dehydration reaction,[4] we, as did Forster, found arresting; consequently we took up the matter, which seemingly had lain unattended since 1922.[5]

Since there has been recorded more chemical information about anhydro-II, this isomer appeared better suited for initial study. Forster reported that, in addition to hot hydrochloric acid, various mild bases such as hydroxylamine, phenylhydrazine and alcoholic ammonia served to convert anhydro-I to -II,[4] and we have observed that the change can be brought about by heat alone. It is recorded that anhydro-II melts at 240° and is optically inactive. The substance was negative in the Liebermann nitroso reaction and was stable to bromine, permanganate and zinc dust and acetic acid. A benzoyl derivative resulted from treatment with benzoyl chloride. But by far the most provocative and valuable of Forster's observations is the change engendered by refluxing dilute aqueous alkali: *anhydro-II, as well as anhydro-I, was cleaved to formic acid and a liquid nitrile possessing the formula* $C_9H_{13}N$.[2] The latter substance, on hydrolysis with alcoholic alkali, led successively to the amide and acid.[6] The end product, isomeric with α-campholytic acid (VIII) and isolauronolic acid (IX), was transformed by mineral acid into the lat-



ter of these two previously known substances. Of the structures for the C_9-nitrile which can accommodate these results (*e.g.*, X-XII), 2,2-dimethyl-3-



methylenecyclopentanecarbonitrile (X) has been established as correct, in that ozonization led to formaldehyde and the known 2,2-dimethyl-3-ketocyclopentanecarboxylic acid (XIII).[7,8] The

(1) Wisconsin Alumni Research Foundation Research Assistant.

(2) M. O. Forster, *J. Chem. Soc.*, **75**, 1141 (1899).

(3) M. O. Forster and W. Robertson, *ibid.*, **79**, 1003 (1901).

(4) M. O. Forster, *ibid.*, **79**, 653 (1901).

(5) P. M. Ginnings with W. A. Noyes, THIS JOURNAL, **44**, 2567 (1922).

(6) M. O. Forster, *J. Chem. Soc.*, **79**, 108 (1901).

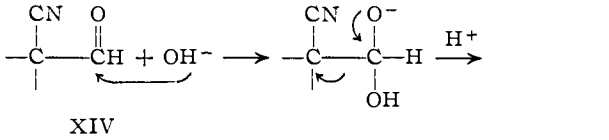
(7) Experimental result obtained in this Laboratory and also reported as an undocumented item by J. L. Simonsen "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949, p. 367.

(8) Before obtaining the new C_9-acid corresponding to the C_9-nitrile, Forster erroneously believed[2] that he had in hand the previously unknown nitrile (and amide) of α-campholytic acid (VIII). Later G. Blanc (*Bull. soc. chim.*, **23**, 695 (1900)) reported that sodium and alcohol reduction of Forster's nitrile afforded α-aminocampholene, identical with the product of hypohalite degradation of α-campholenamide, which at that time Blanc believed to possess structure i. The α-campholenamide structure was soon revised to ii, however; and Forster, on the basis of Blanc's experimental finding, therefore assigned[6] structure iii to his nitrile ("infracampholenonitrile"). Forster was then compelled to "revise" the structure for campholytic acid which is now known to be correct, and he regarded it as best represented by iv. With the structures of all these substances now estab-

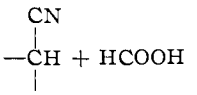
structure assignment was in agreement with the ultraviolet spectrum, showing no selective absorption, and the infrared spectrum, which revealed the nitrile function (4.48 μ) and the terminal methylene grouping (6.08 and 11.27 μ).

The nature of the reactive centers in anhydrobromonitrocamphane-II was clarified by means of its infrared spectrum: well-defined peaks at 2.80 and 4.48 μ definitely indicated the presence of hydroxyl and nitrile functions. Furthermore, the anhydro compound was virtually transparent in the ultraviolet, and infrared bands indicative of a terminal methylene grouping were absent; thus it appeared that this molecule was saturated. Forster's conversion of anhydro-II to a benzoyl derivative (absorption at 4.48 and 5.82 μ) also points to a hydroxyl substituent, and this conclusion has been supported further by the preparation of a methanesulfonate.

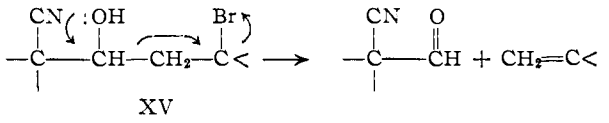
By incorporating the above information into a mechanistic scheme which satisfactorily accounts for (1) the conversion by base to the C_9-nitrile and formic acid and (2) appearance of an unconjugated terminal methylene grouping, only several possible structures for anhydro-II can be derived. It appears most logical that formic acid would arise by hydrolytic cleavage of an α-formylnitrile (XIV). The system XIV is not present *per se* in anhydro-



XIV

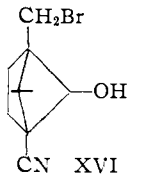


II; however, its transient appearance can be accounted for by *a 1,4-elimination with cleavage of a β-hydroxy-δ-bromonitrile* (XV),[9] which process at

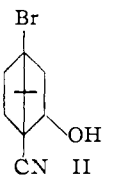


XV

the same time generates the required olefinic linkage. Application to the case under consideration leads to the formulations XVI and II for anhydro-II. Now, chromic acid oxidation afforded a crys-



XVI

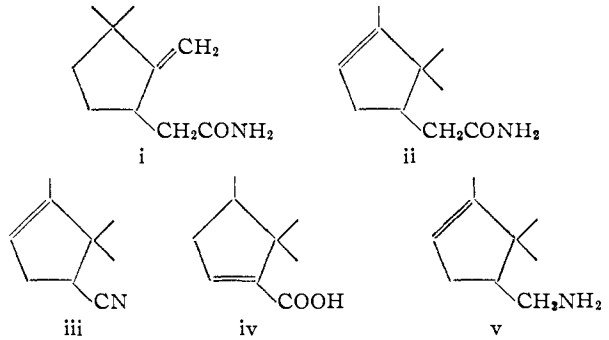


II

talline ketone, m.p. 237°, which regenerated anhydro-II in high yield on reduction with sodium borohydride. The infrared absorption of the ketone featured bands at 4.48 μ—indicating that the nitrile portion had not been modified—and at 5.71 μ, revealing the presence of a cyclopentanone system, a result at variance with that anticipated for structure XVI. Apart from this, the indifference of anhydro-II toward hot silver nitrate is difficult to accommodate on the basis of XVI; II, however, bears a bridgehead halogen, well-recognized for its inertness under SN1 conditions.[10]

Although II (2-hydroxy-4-bromoapocamphane-1-carbonitrile) remains as the solely acceptable structure for anhydro-II, independent confirmation of the proposal was sought. The carbon–oxygen system of camphor is, of course, present, and it seemed that conversion to some appropriate member of that family would serve admirably as a structural proof. In that regard we faced hydrogenolytic removal of the bridgehead halogen, which we contrived to effect through the use of a non-nucleophilic agent, *e.g.*, sodium and alcohol, a reducing device already proved successful for this particular purpose.[11] In order to obviate the elimination reaction of anhydro-II, an almost certain consequence of employing the basic reducing agent, the hydroxyl group was protected by conversion to the tetrahydropyranyl ether (XVII).[12] Hydrogenolysis and

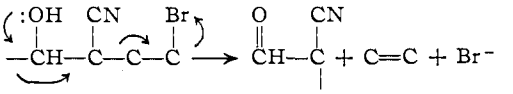
lished beyond question. Blanc's reported conversion of "infracampholenonitrile" to α-aminocampholene (v) remains enigmatic.



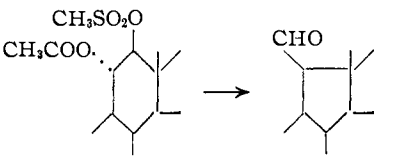
Despite the conflicting and insufficient evidence, structure X has been assumed to represent Foster's nitrile (Beilstein's "Handbuch der Organischen Chemie," Vol. IX, Julius Springer, Berlin, 1926, p. 61; E. Josephy and F. Radt, Elsevier's "Encyclopedia of Organic Chemistry," Ser. III, Vol. 12A, Elsevier Publishing Co., Inc., New York, N. Y., 1948, p. 600).

(9) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955).

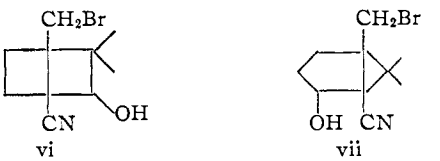
(10) In a related, but less likely, process, a β-cyano-δ-bromo alcohol eliminates, accompanied by bond migration from the alcoholic carbon



(Witness the base-induced rearrangement observed in the steroid



series (N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, THIS JOURNAL, **77**, 1632 (1955)). The implied structures vi and vii are unacceptable, however, because of the same considerations

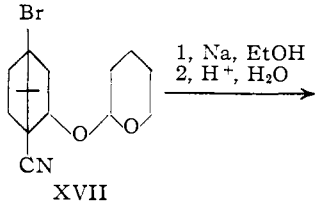


which allow elimination of XVI.

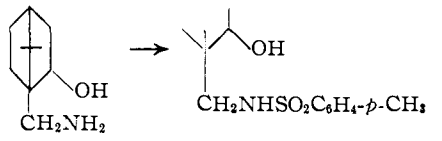
(11) G. Komppa and T. Hasselstrom, *Ann.*, **496**, 164 (1932).

(12) W. E. Parham and E. L. Anderson, THIS JOURNAL, **70**, 4187 (1948).

reduction of the nitrile to a primary amino group were effected simultaneously; and the intermediate ether was hydrolyzed without isolation to the free aminoalcohol XVIII, which in turn was converted

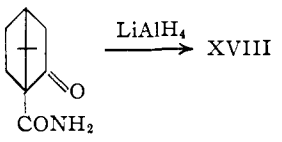


XVII



XVIII XIX

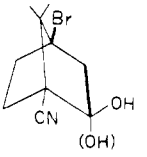
directly to the crystalline *p*-toluenesulfonamide XIX, m.p. 165–166°. This same sulfonamide was found to be derivable from the well-known ketopinic acid.[13] Preparation of ketopinamide (XX) was followed by lithium aluminum hydride reduction; the *p*-toluenesulfonamide of the resulting aminoalcohol was found identical with the corresponding



XX

derivative secured from anhydro-II. The sulfonamide was characterized by chromic acid oxidation to a crystalline ketone, which displayed carbonyl absorption in the infrared at 5.8 μ.

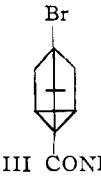
The stereoelectronic demands of the elimination reaction leading to the C_9-nitrile are satisfied by the proposed structure—halogen as well as carbons 2, 3 and 4 describe a plane, as illustrated in XXI.



XXI

Although the carbon–oxygen bond cannot lie in this plane, its geomtery is probably not critical for the elimination[14]; conversely, no conclusion regarding the configuration of the hydroxyl can be drawn from the elimination result.

During the period when we were gathering evidence bearing on the structure of anhydrobromonitrocamphane-I (*vide infra*), its reconstitution from anhydro-II was attempted. Concentrated sulfuric acid, acting for three days at room temperature on the stabler anhydride, did indeed bring about a change, although examination of the product showed it to be a *new isomer* (m.p. 201–202°), which was designated as *anhydrobromonitrocamphane-III*. Simple diagnostic tests revealed the substance to be neutral, and stable to bromine, chromium trioxide or permanganate in the Baeyer test; and infrared spectral analysis led to the conclusion that a primary amide (6.08 and 6.41 μ) grouping was present. Confirmation of this structural feature was found by conversion with nitrous acid to a carboxylic acid which, as its methyl ester, was reduced by lithium aluminum hydride to an alcohol, characterized as a 3,5-dinitrobenzoate. The chemistry described is well accommodated by the structure III for anhydro-III, which arises by



III

controlled nitrile hydrolysis accompanied by 2,6-dehydration with formation of a cyclopropane ring.[15] The formulation III (4-bromotricyclenamide) is strengthened by the persistence throughout the series of a strong band at *ca.* 10 μ, attributable to the presence of the three-membered ring.

Anhydrobromonitrocamphane-I is a colorless substance which does not melt, but at 210–220° decomposes and rearranges in part to anhydro-II. Forster, in his initial report dealing with this dehydration product,[2] listed the following properties: negative Liebermann nitroso test; stability to cold concentrated nitric acid, hot concentrated sulfuric acid, boiling pyridine and bromine in chloroform; oxidation by permanganate in dilute sulfuric acid. Like anhydro-II, the precursor was optically inactive.

Our own investigations started, again, with a spectral examination: the ultraviolet spectrum showed a single band at 225 mμ (ϵ 2300); in the infrared there was no evidence of hydroxyl or nitrile absorption but rather a medium peak at 6.40 μ, suggestive of a carbon–nitrogen double bond.

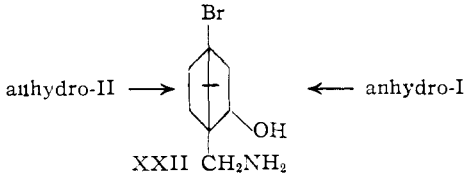
Since anhydro-I is transformed readily to -II (or products derived from -II[4]), acquisition of chemical evidence for the structure of the former under as mild conditions as possible was desirable. Reduction seemed most promising, and we accordingly studied the catalytic hydrogenation, as well as lithium aluminum hydride reduction, of the parent anhydride. The hydride reaction, carried out under normal conditions, provided a mixture of products, from which were separated two crystalline materials. One of these, isolated in about 20% yield, was indicated by analysis to be a dihydroanhydro-I, which was not investigated further. The second product, a base formed in 60% yield, was readily recognized as a tetrahydroanhydro-I and was characterized by conversion to N-toluenesulfonyl and N-benzoyl derivatives. The catalytic reduction of anhydro-I in ethanol–sulfuric acid proceeded to give a tetrahydro product, isolated as the sulfate salt, which was converted directly to an N-benzoyl derivative identical with that secured from the hydride reduction. This amine appeared to be a *bona fide* reduction product of anhydro-I, in that

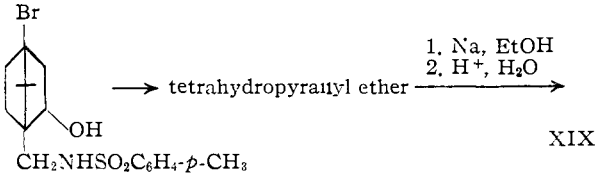
(13) P. D. Bartlett and L. H. Knox, THIS JOURNAL, **61**, 3184 (1939).

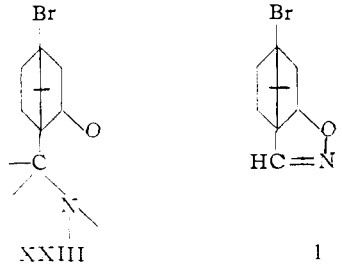
(14) Pointed out by Professor John D. Roberts, California Institute of Technology.

(15) *Cf.* the dehydration of 2-hydroxyapocamphane-1-carboxylic acid to tricyclenic acid (P. Lipp, *Ann.*, **402**, 343 (1902)).

the latter remained unaltered when subjected, in the absence of hydrogen, to the catalytic hydrogenation conditions used. Structure assignment to the tetrahydro compound was made possible by the finding that *this same base resulted from lithium aluminum hydride or catalytic reduction of anhydro-II*—only the aminoalcohol formulation XXII is reasonable. This assignment was confirmed by relating the amine to one of already demonstrated structure. The sulfonamide of the tetrahydro compound, after conversion to the tetrahydropyranyl ether, was reductively debrominated by sodium and alcohol; mild acid hydrolysis then yielded the sulfonamide XIX of the same amine secured by hydride reduction of ketopinamide. These findings led to the important conclusion that *anhydro-I and -II possess the same carbon–oxygen–nitrogen skeleton (XXIII)*.

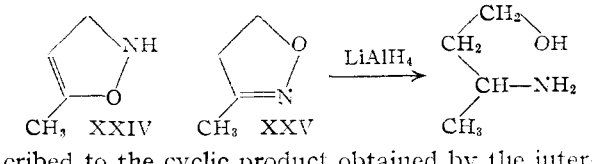


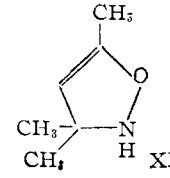




Moreover, the molecular formula requirement, taken together with the absence of –NH, –OH and –CN stretching absorption in the infrared region, invalidate all sterically possible structures for anhydrobromonitrocamphane-I but one: *the isoxazoline* (I).

In order to consolidate the evidence bearing on this proposal, we set about to gather, from model compounds, information which would impart significance to the spectral properties of anhydro-I. Unfortunately, there appeared to be no information available on the spectral behavior of oxime-O-ethers, and the literature seemed wanting in examples of purely aliphatic Δ^2-isoxazolines to which structures had not been assigned arbitrarily or on the basis of meager evidence. For example, the structure XXV rather than XXIV has been ascribed to the cyclic product obtained by the interaction of hydroxylamine with methyl β-chloroethyl ketone[16]; contrarily, elsewhere the inorganic reagent is claimed[17] to convert mesityl oxide to the Δ^4-isoxazoline XXVI. The surmise XXV was vindicated in this Laboratory by lithium aluminum hydride reduction of the heterocycle; 3-amino-1-butanol was produced, identical with material prepared by hydride reduction of ethyl *dl*-β-aminobutyrate.





Whereas anhydro-I displayed a peak in the infrared at 6.40 μ, acetoxime's carbon–nitrogen stretching was reflected by a band at 6.01 μ and that of 3-methyl-Δ^2-isoxazoline (XXV), at 6.17 μ. In the ultraviolet region, acetoxime-O-acetic acid[18] absorbed in the shorter wave length region without indication of a peak; the isoxazoline, however, possesses a band at 212 mμ (ϵ 2830). Thus the models and anhydro-I constitute, in both the infrared and ultraviolet regions, a short graded series with the terpenoid absorbing at the longest wave length in each case. Although no thorough analysis was carried out, it seems reasonable that the observed values are reflections of strain, absent in the acyclic cases, but increasingly consequential in the cycles XXV and I. Molecular models of the last structure showed decided bond angle distortion, apparently relieved by electronic displacement and thus accounting for the lower energy requirements for absorption in the ultraviolet. At the same time, the infrared values cited parallel those recorded for cycloalkenes and cyclic imines of medium ring size.[19]

Justification of structure I, insofar as rational conversion to anhydro-II is concerned, offers no great problem. The acid-catalyzed process may be represented by scheme XXVII, whereas the change initiated by base is symbolized by the process XXVIII.[20] Undoubtedly elimination is facilitated by release of the internal strain afflicting the starting isomer.

Inspection of models verifies that an isoxazoline I utilizing an *endo* bond for attachment of oxygen is almost impossibly strained. Accordingly the stereochemistry of anhydro-I can be depicted by

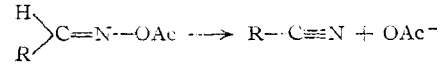
(16) E. E. Blaise and M. Maire, *Compt. rend.*, **142**, 216 (1899).

(17) C. Harries and L. Jablonski, *Ber.*, **31**, 1376 (1898).

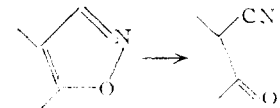
(18) The 6μ region of acetoxime-O-acetic acid is uninformative, because of the broad carbonyl base.

(19) B. Witkop, THIS JOURNAL, **78**, 2873 (1956).

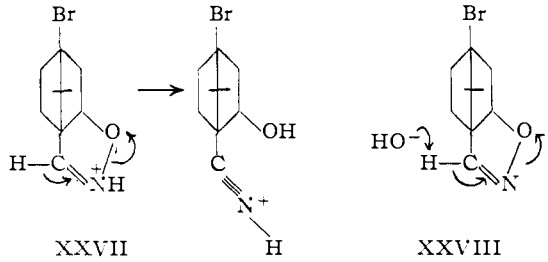
(20) Elimination of acetic acid from aldoxime acetates yields



nitriles, and many isoxazoles (viii) isomerize to the ketonitriles (W. S. Johnson and W. E. Shelberg, *ibid.*, **67**, 1745 (1945)). Both processes are brought about by base.



viii

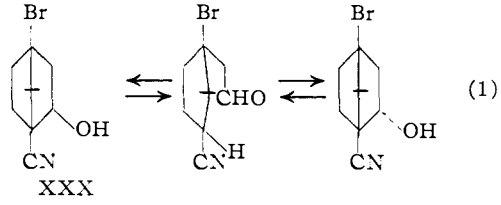


XXVII XXVIII

formula XXIX, *i.e.*, involving fusion of the hetero-

XXIX XXX

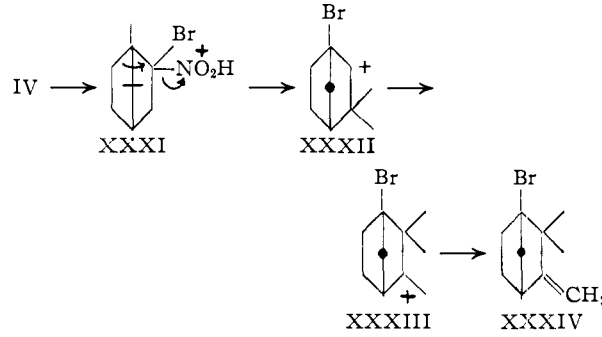
cyclic ring to the camphane system through an *exo* bond, an arrangement still implying definite distortion. The stereochemistry of anhydro-II cannot be disposed of so easily. If, in proceeding from I to II, we assume that no change other than that described by the mechanism considered above (XXVII or XXVIII) occurs, the stereochemical integrity of the hydroxyl group will be maintained, and the configurational assignment XXX is automatic. On the other hand, a subsequent equilibrium system (1) involving the bicyclic hydroxynitrile and the



XXX (1)

monocyclic aldehydronitrile is conceivable and would provide for conversion of the *exo* (less stable[21]) configuration of XXX to the *endo*. The regeneration of anhydro-II through sodium borohydride reduction of the corresponding ketone, a reaction which parallels the lithium aluminum hydride reduction of camphor to isoborneol,[22] also implies, in the simplest interpretation, the *exo* configuration. However, the case is again weakened by the same equilibrium consideration. A secure stereochemical assignment is made possible by reference to the hydrogenation results already detailed. Both anhydro compounds yield the same tetrahydro isomer, which is no longer epimerizable at C-2; since the hydrogenation conditions used are not likely to effect inversion at some intermediary stage,[23] oxygen attachment is *exo* (XXX) in anhydro-II, as in -I. Corollarially, the aldo-type equilibrium (1) considered above cannot intervene to the extent that any detectable amount of the more stable *endo* isomer of anhydro-II accumulates. Further, the hydride reduction of the ketones in this series must then, as in the camphor case, provide the less stable of the possible diastereoisomeric alcohols.

Associated with the structural clarification of anhydro-I is the more fundamental problem of its formation, a change involving a seemingly random reshuffling of non-skeletal atoms. Some order can be gained by considering, first of all, a series of Wagner–Meerwein shifts initiated by attachment of a proton to the nitro group of the starting material (XXXI). Nitrous acid, or its equivalent, is ex-



XXXI XXXII XXXIII XXXIV

pelled and may remain associated with the cation, although its sphere of activity in these early stages is obscure. Production of the isocamphane skeleton involves a migration of methyl (XXXII → XXXIII) followed by elimination of a proton to give 4-bromocamphene (XXXIV). ω-Nitrosation ensues, yielding XXXV or XXXVI, and this recombination is followed by a second skeletal rearrangement, as expressed by the formulas (XXVI → XXVII). Closure (XXVII) of the isoxazoline ring (which one would anticipate to give the stabler form (*exo*) of I) completes the sequence.[24]

Earlier it was noted that both I and II are optically inactive. This property can be best accounted for by assuming 2,6-hydrogen transfer at the stage XXXVII, resulting in racemization, either through simple enantiomer production (XXXVII → XXXVIII) or by way of a symmetrical cation.[25,26]

It is possible that reactions in the terpene series similar to those described above have been carried out but gone unrecognized. For example, Konovalov,[27] in 1902, recorded the conversion of camphene by dilute nitric acid at 100° to an oxidation product $C_{10}H_{15}NO$ (m.p. 266–267°). The substance was said to be stable in the bromine and permanganate tests but susceptible to the action of sodium and alcohol. More drastic acid conditions effected transformation to tricyclenic acid (XXXIX). These data, admittedly scanty, are interpretable

(21) Borneol (*endo*) is more stable than isoborneol (*exo*): J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949, pp. 351–353.

(22) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 475.

(23) This same reaction cannot, in fact, be operative since the same aminoalcohol is secured from anhydro-II tetrahydropyranyl ether (XVII), which is not susceptible to the heavy-metal catalyzed, oxidation–reduction equilibrium necessary for inversion under these conditions.

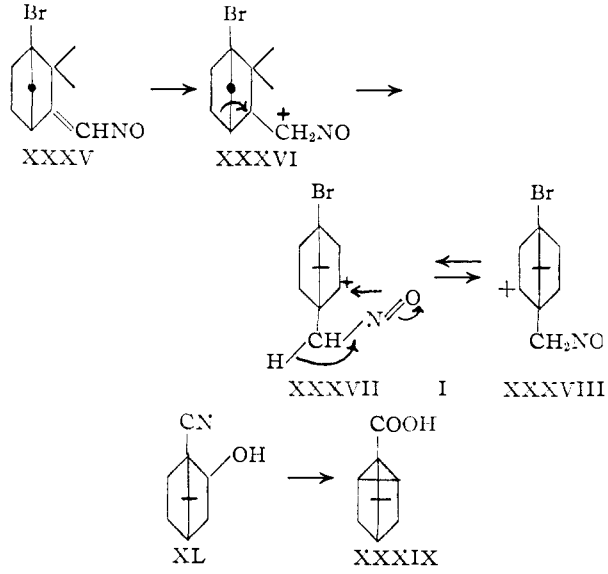
(24) Certain features of this over-all change find analogy in, *e.g.*, the formation of β-camphor dichloride (J. Houben and E. Pfankuch, *Ann.*, **501**, 219 (1933)) and camphor-10-sulfonic acid (E. Wedekind, D. Schenk and R. Stusser, *Ber.*, **56**, 633 (1923)) from camphor.

(25) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., THIS JOURNAL, **76**, 4501 (1954).

(26) The most recent publication[5] dealing with anhydro-I or -II describes the action of methylmagnesium iodide on -I. The intermediate ($C_{11}H_{18}ONBr$) was reported to undergo hydrolysis with alkali, affording 1,2,2-trimethyl-3-acetylcyclopentanecarboxylic acid. However, the final product was not compared with authentic material, nor was an analysis reported; consequently, we do not believe that this claim need be reconciled with the findings and conclusions reported in this contribution.

(27) Konovalov, *J. Russ. Phys. Chem. Soc.*, **34**, II, 43 (1902).

in terms of the structure XL, arising along lines considered above. Konovalov further states that, on treatment with fuming nitric acid, the $C_{10}H_{15}NO$ compound gave rise to a product $C_{10}H_{14}N_2O_3$, which regenerates the starting material on reduction with



tin and hydrochloric acid. A similar pair of reactions characterizes anhydrobromonitrocamphane-II,[2] and the infrared behavior indicates that the nitro derivative is merely the O-nitrate. This explanation is of course equally applicable to the Konovalov case.

Experimental[28]

Anhydrobromonitrocamphane-I.—A solution of 43 g. (0.16 mole) of bromonitrocamphane in 100 ml. of petroleum ether was dropped slowly into a vigorously stirred mixture of 300 g. of concentrated sulfuric acid and 50 ml. of petroleum ether held at −5°. After the addition was complete, the mixture was stirred an additional 0.5 hr., then poured on crushed ice. In order to obtain even fairly good crude material, it was found necessary to wash the precipitated product with dilute ammonia as it was being filtered, since it turned dark brown otherwise. This is in contrast to the experience of Ginnings and Noyes,[5] who state that the product precipitates "as a slightly yellow flocculent solid in nearly quantitative yield, pure enough for most purposes." Recrystallization from ethanol gave in general 18–25 g. of crude product (46–60%).

Anhydrobromonitrocamphane-II.—Refluxing a solution of 10 g. of anhydro-I in 30 ml. of 95% ethanol containing 5 ml. of 12 *N* hydrochloric acid gave anhydro-II essentially quantitatively; m.p., after recrystallization from ethanol-water, 244–245°.[2]

Treatment of II with methanesulfonyl chloride in dry pyridine gave a mesylate as needles from benzene–petroleum ether, m.p. 101–102°.

Anal. Calcd. for $C_{11}H_{16}O_3NSBr$: C, 41.00; H, 5.01. Found: C, 41.06; H, 4.75.

Heating II with fuming nitric acid for 10 minutes on the steam-bath gave a nitrate ester as needles from ethanol, m.p. 99–100°. Infrared bands at 6.07, 7.80 and 11.5 μ could be assigned to the nitrate grouping.

Anal. Calcd. for $C_{10}H_{13}O_3N_2Br$: C, 41.54; H, 4.53. Found: C, 41.59; H, 4.49.

Anhydro-II Ketone.—Anhydro-II (2.4 g., 0.01 mole) was dissolved in 50 ml. of glacial acetic acid and was added with stirring to a cooled mixture of 1.0 g. (0.01 mole) of chromium trioxide in 100 ml. of glacial acetic acid. The mixture was stirred 2 hr. at room temperature; it was then poured into cold water, and the product was collected by filtration and recrystallized from 95% ethanol (prisms). The yield in several runs was 2.1–2.3 g. (85–95%), m.p. 237°. A carbonyl band at 5.71 μ indicated a five-membered ring ketone.

Anal. Calcd. for $C_{10}H_{12}ONBr$: C, 49.55; H, 4.99. Found: C, 49.83; H, 5.20.

Treatment of 120 mg. (0.5 mmole) of the ketone with a slurry of excess sodium borohydride in a mixture of ethanol–ether for 1 hr. gave a solid, m.p. 235–238°, after decomposition of the excess hydride with dilute hydrochloric acid and the usual work-up. One recrystallization from ethanol gave 110 mg. (92%) of solid, m.p. and mixed m.p. with authentic anhydro-II 244–245°. About 4% starting material was recovered from the mother liquors, m.p. 235–237° (no depression on admixture with authentic ketone).

2,2-Dimethyl-3-methylenecyclopentanecarbonitrile (X).—When either anhydro-I or anhydro-II was treated with excess 30% sodium hydroxide at reflux temperature for 1 to 2 hr., steam distillation of the reaction mixture and extraction of the distillate with ether followed by the usual drying and distillation afforded *ca.* 40% of a sweet-smelling, mobile oil, b.p. 81° (16 mm.), $n^{25}D$ 1.4620.[2]

Ozonolysis of X.—A moderate excess of ozone was passed into a solution of 1.1 g. of nitrile X (0.00815 mole) in 50 ml. of cooled glacial acetic acid. Half this solution was poured into a 250-ml. flask containing 50 ml. of water and 2 g. of zinc dust; the mixture was steam distilled under nitrogen until 110 ml. of distillate was collected. Half of this was refluxed for 10 minutes with 1.0 g. of dimedon, 20 ml. of ethanol and 3 drops of pyridine and allowed to stand overnight in the cold. The other half was treated with 50 ml. of dimedon reagent, neutralized with 5 ml. of 5% hydrochloric acid and also allowed to stand in the ice-box overnight. The combined yield of adduct was 0.365 g., 25% of theory, m.p. and mixed m.p. with an authentic sample of dimedon–formaldehyde 189–191°.[29] To characterize the other fragment of the ozonolysis, a solution of 1.1 g. of X in glacial acetic acid was prepared and ozonized as above. The solution was then refluxed with 100 ml. of water and 4 g. of zinc dust for 15 minutes. Cooling, extraction with ether and the usual workup gave about 650 mg. of an oil whose infrared spectrum indicated a five-membered ring ketonitrile. This oil was refluxed with 20 ml. of 25% sodium hydroxide until the oil disappeared. The solution was cooled, acidified and extracted repeatedly with ether. Drying and evaporation of the ether yielded about 200 mg. of a glass which solidified on rubbing with cold methanol. It sublimed readily at 0.3 mm. on the steam-bath to give XII, m.p. 104–105°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.95; H, 7.93.

The material was characterized by the preparation of an oxime, m.p. 195°, and a semicarbazone, m.p. 219–220°. Perkin and Thorpe[30] gave the following melting points for 2,2-dimethyl-3-ketocyclopentanecarboxylic acid: acid, 108–109°; oxime, 198°; semicarbazone, 215°. A mixed melting point of our material with authentic ketoacid XII was undepressed.[31] The infrared spectra were identical.

Anhydrobromonitrocamphane-III.—When anhydro-II was allowed to stand three days at room temperature in concentrated sulfuric acid, a product was obtained on pouring the sulfuric acid solution into cold water and recrystallizing the precipitate from ethanol. A sample recrystallized from ethanol for analysis melted at 201–202° (prisms).

Anal. Calcd. for $C_{10}H_{14}ONBr$: C, 49.18; H, 5.74. Found: C, 49.32; H, 5.81.

This material was further characterized as follows: treatment of a solution of the amide in dry chloroform in the presence of anhydrous sodium carbonate with nitrogen dioxide,[32] followed by acidification, drying and evaporation of the solvent, gave an acid. This acid was quantitatively

(28) Infrared spectra were taken on a Baird recording infrared spectrophotometer. Ultraviolet spectra were measured with a Cary spectrophotometer, on samples dissolved in ethanol.

(29) P. Karrer and J. Kebrle, *Helv. Chim. Acta*, **35**, 863 (1952).

(30) W. H. Perkin, Jr., and J. F. Thorpe, *J. Chem. Soc.*, **85**, 138 (1904).

(31) C. S. Gibson, K. V. Hariharan and J. L. Simonsen, *ibid.*, 3009 (1927).

(32) E. White, THIS JOURNAL, **76**, 4497 (1954).

esterified with diazomethane in ether solution to give a methyl ester, m.p. 69° (sublimed).

Anal. Calcd. for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.84. Found: C, 50.64; H, 5.80.

This methyl ester was converted to the alcohol by treatment with excess lithium aluminum hydride in dry ether in the usual manner. The product (feathery needles from ethanol) melted sharply at 160° (87% yield). Conversion to a 3,5-dinitrobenzoate by treatment with the corresponding chloride in dry pyridine gave material, m.p. 124–125° (leaflets from ethanol–water).

Anal. Calcd. for $C_{17}H_{17}O_6N_2Br$: C, 48.01; H, 4.03. Found: C, 48.46; H, 4.19.

Conversion of Anhydro-II to 2-Hydroxy-10-aminocamphane (XVIII).—Anhydro-II, 2.0 g. (0.0082 mole), was dissolved in 20 ml. of alcohol-free chloroform. To this was added 1.0 g. of dry, redistilled dihydropyran followed by four drops of concentrated hydrochloric acid and approximately 1 g. of anhydrous sodium sulfate.[12] The mixture was stirred 3 hr. at room temperature, then shaken with two 10-ml. portions of 30% sodium hydroxide. Ether was added and the organic layer washed with water. The usual work-up gave 2.3 g. of tetrahydropyranyl ether (XVII), m.p. 120–130°, star-shaped clusters of needles from hexane (89% yield).

The ether (1.76 g., 0.0054 mole) was dissolved in 75 ml. of refluxing absolute ethanol and 5 g. of sodium added in small pieces over a period of 2 hr. The solution was made acid to congo red with concentrated hydrochloric acid in ethanol (cooling), concentrated *in vacuo* on the steam-bath; the residue was taken up in water and extracted with ether. The aqueous layer was made basic with 10% sodium hydroxide and thoroughly extracted with ether. Drying and evaporation of the ether gave about 350 mg. of a slightly greenish oil. The yield is 39%. The material readily was converted with tosyl chloride in pyridine (or with 20% sodium hydroxide) to a sulfonamide (XIX), m.p. 165–166°, leaflets from ethanol–water. A sample was recrystallized from ethyl acetate for analysis (prisms).

Anal. Calcd. for $C_{17}H_{25}O_3NS$: C, 63.14; H, 7.79. Found: C, 63.45; H, 7.56.

Oxidation of XIX.—The sulfonamide (140 mg., 0.41 mmole) was dissolved in 10 ml. of glacial acetic acid, and 50 mg. (0.5 mmole) of chromic anhydride was added in small portions. The mixture was stirred magnetically at room temperature for an hour, then poured onto ice and extracted with ether. The usual workup gave 86 mg. of ketone, m.p. 130–133° (62% yield). After recrystallization from ethanol–water and then ethyl acetate, it melted at 144–146° (short rods).

Anal. Calcd. for $C_{17}H_{23}O_3NS$: C, 63.53; H, 7.21. Found: C, 63.66; H, 7.31.

Conversion of Ketopinic Acid to XVIII.—Ketopinamide was prepared by treatment of an ether solution of the acid chloride with a stream of anhydrous ammonia.[33] After evaporation of the ether and excess ammonia, the residue was treated with hot ethyl acetate. Inorganic material was removed by filtration, and the solution was evaporated to dryness, taken up in benzene and evaporated to dryness again. On trituration with petroleum ether, a nicely crystalline product was obtained, m.p. 190–194°, 4.6 g., 92% from 5.0 g. of acid. The amide is extremely soluble in cold water. Ketopinamide (1.50 g., 0.00825 mole) was dissolved in 25 ml. of dry tetrahydrofuran and added to a slurry of 2 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The mixture was refluxed with stirring under nitrogen for 2 hr. The usual workup gave about 1.2 g. of a slightly yellow oil. This was not purified but treated immediately with 25 ml. of 20% sodium hydroxide and 2 g. of tosyl chloride. The originally oily mixture solidified, on warming, after 10 minutes. After all excess tosyl chloride had decomposed, the precipitate was filtered, washed and dried to yield 2.25 g. of crude tosylamide, m.p. 153–156° (85%). On recrystallization from ethanol–water and then ethyl acetate, the m.p. was raised to 165–166°, and a mixed melting point with II gave no depression. The infrared spectra of the compounds were identical.

Anal. Calcd. for $C_{17}H_{25}O_3NS$: C, 63.14; H, 7.79. Found: C, 62.94; H, 7.86.

(33) E. Wedekind, *Ber.*, **57**, 664 (1924).

Oxidation with chromic anhydride in glacial acetic acid yielded a ketone, m.p. 144–145° after recrystallization from ethanol–water, identical (mixed m.p., infrared) with the corresponding ketone prepared from authentic XIX (see above).

Tetrahydroanhydro-II (XXII).—Anhydro-II (1.076 g., 0.00441 mole) was hydrogenated at atmospheric pressure in the presence of *ca.* 0.2 g. of prereduced platinum oxide in 95% ethanol; 93% of 2 moles of hydrogen was absorbed in 11 hr. (For no apparent reason, the reaction was sometimes complete, on approximately the same amounts of material, in 5 hr.) Workup yielded 980 mg. of an amine, m.p. after recrystallization from ethyl acetate–petroleum ether, 183–184°.

Anal. Calcd. for $C_{10}H_{18}ONBr$: C, 48.39; H, 7.31. Found: C, 48.15; H, 7.22.

The compound was characterized by the formation of a benzamide (with benzoyl chloride in dry pyridine) which crystallized as thin, rectangular plates from ethyl acetate–petroleum ether, m.p. 219–220°.

Anal. Calcd. for $C_{17}H_{22}O_2NBr$: C, 57.96; H, 6.29. Found: C, 57.70; H, 6.37.

Reduction of Anhydro-II with Lithium Aluminum Hydride.—When anhydro-II (1.5 g.) was reduced with an excess of lithium aluminum hydride in dry ether in the usual manner, it yielded 1.44 g. (95%) of an amine, m.p. 184° (plates from ethyl acetate–petroleum ether), identical in all respects with XXII.

Tetrahydroanhydro-II Sulfate from Anhydro-I.—When 900 mg. (0.0037 mole) of anhydro-I was dissolved in 95% ethanol containing an equimolar amount of sulfuric acid and the mixture hydrogenated as above (cooling), 2 moles of hydrogen were absorbed in 1 hr. The crude amorphous product crystallized as small plates from a mixture of ethanol and water containing a little sulfuric acid, m.p. *ca.* 318° (with vigorous decomposition).

Anal. Calcd. for $C_{20}H_{38}O_6N_2Br_2S$: C, 40.42; H, 6.44. Found: C, 40.35; H, 6.40.

To check the possibility that anhydro-I might have isomerized under the conditions of the reduction, 244 mg. (1 mmole) was stirred with 1 mmole of sulfuric acid in 25 ml. of 95% ethanol containing 50 mg. of platinum oxide for 3 hr. at room temperature. The usual workup and one recrystallization from ethanol gave material which was apparently pure anhydro-I according to its infrared. It showed characteristic anhydro-I behavior on melting.

Treatment of Anhydro-I with Lithium Aluminum Hydride.—Reduction of 2.03 g. of anhydro-I with excess lithium aluminum hydride in ether yielded, after the usual workup, 1.91 g. of crude amorphous product, m.p. 110–130°. This was chromatographed with chloroform on silicic acid to yield 75% of XXII and 25% of another compound, which was neutral and analyzed as a *dihydro derivative*, m.p., after several recrystallizations from ethyl acetate, 185–187°.

Anal. Calcd. for $C_{10}H_{16}ONBr$: C, 48.79; H, 6.55. Found: C, 48.90; H, 6.79; infrared spectrum (KBr disk), 3.03, 3.24 sharp, 6.18, 6.40 μ.

Conversion of Tetrahydroanhydro-II to XVIII.—Tetrahydroanhydro-II (160 mg., 0.65 mmole) was treated with tosyl chloride in pyridine; the usual workup gave 180 mg. of tosylamide, m.p. 163–165°, needles from ethanol–water (68% yield). The tetrahydropyranyl ether of this material was prepared by stirring the above with 42 mg. of dihydropyran (0.5 mmole, 0.05 ml.) in 10 ml. of alcohol-free chloroform containing two drops of concentrated hydrochloric acid and a little anhydrous sodium sulfate. After 1 hr., the mixture was poured into cold 10% sodium hydroxide and shaken thoroughly to remove all traces of acid. The crude ether weighed 100 mg., after recrystallization from ethanol. It was then dissolved in absolute ethanol and treated with sodium as previously described. Acidification and the usual workup gave about 50 mg. (80%) of material which, after passage through a silicic acid column and two recrystallizations from benzene–petroleum ether, melted at 165–166° and did not depress the melting point of an authentic sample of XIX. The infrared spectra in chloroform were essentially identical.

Lithium Aluminum Hydride Reduction of 3-Methyl-Δ^2-isoxazoline.—The isoxazoline (6.5 g.) was dissolved in 25 ml. of dry tetrahydrofuran and added to a magnetically-stirred slurry of 1.0 g. of lithium aluminum hydride in 50 ml.

of tetrahydrofuran under nitrogen. The mixture was held at 65° for 0.5 hr., then allowed to stand at room temperature for another hour. Ethyl acetate was added to decompose the excess hydride, followed by saturated sodium potassium tartrate. The solvents were separated from sludge by decantation, the latter extracted with hot alcohol, combined with the former, dried and distilled to give 18% of crude starting material (b.p. 48–53° (8 mm.), $n^{25}D$ 1.4435) and 2.48 g. of 3-amino-1-butanol, b.p. 73–74° (7 mm.) (reported[34] b.p. 82–85° (19 mm.)), $n^{25}D$ 1.4532–1.4543, 48% yield (based on unrecovered isoxazoline). A sample was distilled twice for analysis, precautions being taken to exclude water vapor and carbon dioxide.

Anal. Calcd. for $C_4H_{11}NO$: C, 53.89; H, 12.44. Found: C, 54.15; H, 11.97.

Reduction of Ethyl *dl*-β-Aminobutyrate.—Ethyl β-aminobutyrate (5.0 g., 0.0038 mole), prepared from 3-acetamidocrotonic ester[35] by reduction of the latter according to Skita with platinum oxide in ethanol containing a few drops of concentrated hydrochloric acid, followed by hydrolysis and re-esterification,[36] was reduced with lithium aluminum hydride in ether for 15 minutes according to Karrer.[37] Workup yielded an oil which was rectified in vacuum to give 2.11 g. of an aminoalcohol, b.p. 73° (7 mm.), $n^{25}D$ 1.4534-1.4543 (62%). The infrared of this material (neat) and that from isoxazoline showed little resolution but were superimposable, broad bands centered at 3.15, 6.29, 9.05, 9.40 μ. Samples of both amino alcohols were converted to identical bis-*p*-nitrobenzoyl derivatives, m.p. 155–156°, separately and on admixture. An analytical sample was recrystallized from ethanol (balls of tiny needles, m.p. 157°).

Anal. Calcd. for $C_{18}H_{17}N_3O_7$: C, 55.81; H, 4.42. Found: C, 55.91; H, 4.56.

The aminoalcohol was further characterized as the bis-benzoyl derivative, leaflets from ethanol-water, m.p. 112–112.5°.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.40. Found: C, 72.36; H, 6.37.

(34) Bayer and Co., German Patent 247,144; *Chem. Zentr.*, **83**, 159 (1912).

(35) A. Skita and C. Wulff, *Ann.*, **453**, 206 (1927).

(36) E. Fischer and C. Roeder, *Ber.*, **34**, 3755 (1901).

(37) P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

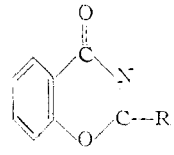
Experiments with 2-Aryl-1,3-benzoxaz-4-ones and with 2-Phenyl-2,3-dihydro-1,3-benzoxaz-4-one. A New Type of Thermochromic Compounds

BY AHMED MUSTAFA AND ALAA ELDIN ABDEL AZIZ HASSAN

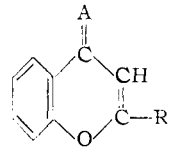
RECEIVED FEBRUARY 5, 1957

A number of new thermochromic di-(2-aryl)-1,3-benzoxaz-4-ylidenes (IVa-c) now have been prepared. Fission of the central ethylene linkage in IVa-c is brought about by the action of sulfur at 250° to yield the corresponding benzoxaz-4-thione derivatives (Va-c), respectively, and by the action of thionyl chloride followed by water in the case of IVa to give 2-phenyl-1,3-benzoxaz-4-one (Ia). The two new benzoxaz-4-one derivatives (Ib-c), needed in this investigation, have been synthesized. Whereas Ia, Ic, Va and/or Vc react with hydroxylamine hydrochloride in the presence of pyridine to give the corresponding oxime derivatives, they react with hydrazine hydrate to yield the corresponding 1,2,4-triazole derivatives (VIa-b), respectively. Treatment with organomagnesium compounds brought about addition to the carbonyl group in the case of Ic and cleavage of the hetero ring in the case of 2-phenyl-2,3-dihydro-1,3-benzoxaz-4-one (X).

2-Aryl-1,3-benzoxaz-4-ones (Ia-c) bear a structural resemblance to flavone (IIa), the former having in the hetero ring the system —CR=N— in place of CR=CH— in the latter. This has stimulated us to investigate the analogy between I and II in their chemical reactions.

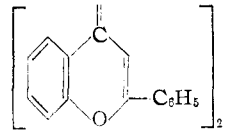


Ia, R = C_6H_5
b, R = $C_6H_4CH_3$-*p*
c, R = $C_6H_4OCH_3$-*p*

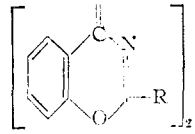


IIa, A = O; R = C_6H_5
b, A = S; R = C_6H_5

Diflavylene (III) shows remarkable physical and chemical properties; it forms light yellow crystals at the temperature of liquid air, at room temperature they are yellow, the melt is ruby-red and the color of the hot solutions varies from orange-red to deep red depending on concentrations.[1] Under pressure, it shows piezochromic properties,[2] changing from yellow to dark red. We now have found that di-(2-aryl)-1,3-benzoxaz-4-ylidenes (IVa-c) show thermochromic properties: dilute solutions of IVa in ethyl benzoate and/or in diphenyl ether are yellow at 0° and orange-red at the boiling point of the solvent; the phenomenon is reversible. Strong thermochromic effects also were observed with powdered solid IVa (yellow at 0° ⟷ deep red at 260°).



III



IVa, R = C_6H_5; b, R = $C_6H_4CH_3$-*p*; c, R = $C_6H_4OCH_3$-*p*

III shows remarkable behavior toward thionyl chloride, followed by the action of water[3] and toward the action of elementary sulfur[4]; fission of the central ethylene bond occurs and IIa and IIb are formed, respectively. We now have found that IVa behaved analogously; fission of the central ethylene linkage in IVa-c is brought about by the action of sulfur at 250° to yield the corresponding benzoxaz-4-thione derivatives (Va-c), respectively, and by the action of thionyl chloride followed by the action of water in the case of IVa to give Ia.

Whereas IIa reacts with hydroxylamine hydrochloride to give the corresponding oxazole deriva-

(1) A. Schönberg and S. Nickel, *Ber.*, **64**, 2325 (1931).

(2) A. Schönberg, A. F. A. Ismail and W. Asker, *J. Chem. Soc.*, 442 (1946).

(3) A. Schönberg and W. Asker, *ibid.*, 272 (1942).

(4) A. Schönberg, *Ber.*, **58**, 1793 (1925).