(b).—A batch of 3.5 g. of crude 4-ethoxy-2,3,6-triaminopyridine dihydrochloride was refluxed with 20 ml. of 98% formic acid for 19 hours. The volatile material was then evaporated and the residue was refluxed for 4 hours with 20 ml. of concentrated hydrochloric acid. Upon removal of the excess hydrochloric acid the residue was taken up with a little water, then made weakly alkaline with sodium bicarbonate. The crystalline material which separated weighed 1.4 g. (57% from nitroso compound). A sample was charcoaled and recrystallized from water, m.p. 238–240°.

Anal. Calcd. for $C_8H_{10}N_4O$: N, 31.4. Found: N, 31.6.

5-Amino-7-hydroxy-1,3,4-imidazopyridine (6-Hydroxy-2-amino-1-deazapurine, 1-Deazaguanine)(XII). (a).—A mixture of 1.1 g. of 6-ethoxy-2-amino-1-deazapurine and 15 ml. of 48% hydrobromic acid was refluxed for 4 hours. The crystalline material which separated on cooling was filtered off (0.8 g.) and dissolved in 5 ml. of water. This solution was neutralized with sodium bicarbonate and the separated solid material was filtered off. The yield was 0.3 g. (29.5%). Recrystallized several times from water, once with the addition of charcoal, deazaguanine was obtained as a monohydrate, m.p. above 300°.

Anal. Calcd. for $C_6H_6N_4O \cdot H_2O$: C, 42.86; H, 4.80; N, 33.3. Found: C, 43.07, 43.11; H, 4.77, 4.86; N, 33.5, 33.2.

(b).—A 4.6-g. sample of 4-ethoxy-2,6-diamino-3-nitrosopyridine was reduced with hydrogen sulfide as above and the reduction product condensed with formic acid. The crude cyclization product was refluxed with 50 ml. of 48% hydrogen bromide for several hours. The crystals were filtered off after cooling, dissolved in a little water and made weakly alkaline with aqueous sodium bicarbonate. A crop of 2.3 g. (54%) of crude material was separated. Recrystallized several times from water, once with charcoal, it was obtained as shiny, colorless leaflets, m.p. above 300°.

Anal. Calcd. for $C_6H_6N_4O \cdot H_2O$: C, 42.86; H, 4.80; N, 33.3. Found: C, 42.94; H, 4.82; N, 33.2.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Willgerodt Reaction with Acylmesitylenes. The Mechanism of the Reaction

BY WILLIAM G. DAUBEN AND JOHN B. ROGAN[1]

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The Willgerodt reaction with acylmesitylenes has been investigated. In all cases, keto-thioamides are formed. Such results suggest that carbonyl addition and reduction are not necessary steps for this reaction and a modification of previously postulated mechanisms is presented.

The mechanism of the Willgerodt reaction has attracted considerable attention during the past decade, and to date there still is doubt as to exactly what processes are involved. To a large degree, this has been due to the failure to isolate intermediates directly[2] or to identify them.

The technique of treating theoretically possible intermediates under conditions of the Willgerodt reaction in order to determine whether or not they are actual possible intermediates has revealed the fact that the reaction is not limited to ketones, as originally supposed, but is applicable to olefins,[2–5] acetylenes,[4,5] alcohols,[3–5] halides,[6] amines[6] and even alkyl-substituted aromatic compounds.[2]

Perhaps the most satisfactory mechanism yet suggested for the conversion of ketones into amides (or thioamides) under Willgerodt conditions is that of King and McMillan[7] which envisions reduction of the carbonyl group to a hydroxyl (or thiol) followed by elimination to an olefin. This latter functional group is regarded as proceeding along the carbon chain by a series of reversible additions and eliminations of hydrogen sulfide until the terminal carbon is reached, at which point irreversible oxidations occurs. A similar mechanism was suggested by Carmack and DeTar[4] except an acetylenic intermediate was postulated.

In any event, both mechanisms require initial attack at the carbonyl group. In an attempt to determine whether or not such a step is in reality a necessary requirement, acetylmesitylene was allowed to react under the conditions of the Willgerodt reaction. The decreased reactivity toward carbonyl addition of such a hindered ketone is well known.[8]

From the reaction of acetylmesitylene, sulfur and morpholine there was isolated an orange-yellow crystalline solid (I) in 34% yield which contained both nitrogen and sulfur. Although no recognizable product could be obtained from acid hydrolysis, prolonged saponification afforded a mixture of an acid (II) and a neutral nitrogen-containing material (III). These latter two compounds were shown to be mesitylglyoxylic acid and its morpholide, respectively, by comparison with authentic samples. When the original reaction product I was allowed to react with Raney nickel, both desulfurization and reduction of the carbonyl group occurred and an amino alcohol IV was obtained. The structure of this material was established as α-mesityl-β-(N-morpholino)-ethanol by comparison with a sample prepared by the lithium aluminum hydride reduction of ω-(N-morpholino)-acetylmesitylene, which in turn was prepared by allowing ω-bromoacetylmesitylene to react with morpholine. On the basis of the foregoing degradations, the acetylmesitylene Willgerodt product can be assigned the structure I.

The compound I may be regarded either as a nor-

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[1] Recipient of the U. S. Rubber Co. Fellowship in Chemistry, 1954-1955.

[2] One notable exception (M. A. Naylor and A. W. Anderson, THIS JOURNAL, **75**, 5392 (1953)) is the isolation of what appears to be diisobutyl disulfide and trisulfide from the reaction of isobutylene, sulfur and aqueous ammonia. These compounds were capable of being transformed into isobutyramide when resubjected to Willgerodt conditions.

[3] J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 525 (1946).

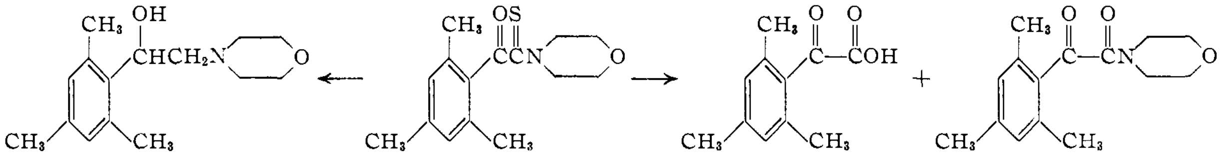
[4] M. Carmack and D. F. DeTar, *ibid.*, **68**, 2029 (1946).

[5] D. B. Pattison and M. Carmack, *ibid.*, **68**, 2033 (1946).

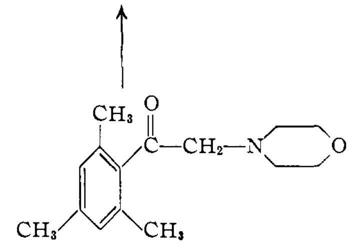
[6] R. T. Gerry and E. V. Brown, *ibid.*, **75**, 740 (1953).

[7] J. A. King and F. H. McMillan, *ibid.*, **68**, 632 (1946).

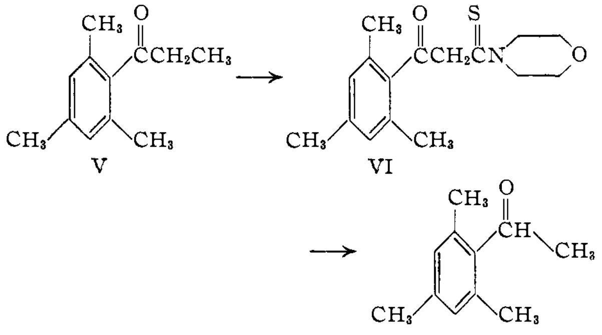
[8] R. C. Kadesch, *ibid.*, **66**, 1207 (1944); L. H. Schwartzman, *ibid.*, **76**, 78 (1954); D. E. Pearson and F. Greer, *ibid.*, **77**, 1294 (1955).



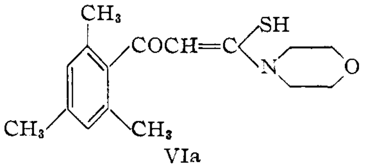
IV I II III



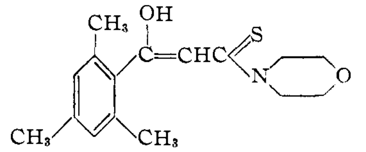
mal Willgerodt product, except that the carbonyl group has been retained, or as a product resulting from the direct oxidation of an active methyl group by sulfur and thus bear no relationship to the Willgerodt reaction. To distinguish between these possibilities, propionylmesitylene (V) was allowed to react with sulfur and morpholine under the same conditions as acetylmesitylene. The product of the reaction was a pale yellow solid containing both nitrogen and sulfur and gave an intense violet ferric chloride enol test and which was soluble in dilute aqueous base. On treatment with acid, the material was both hydrolyzed and decarboxylated to yield acetylmesitylene which, in turn, was identified as the dinitro derivative. On the basis of this degradation sequence and on the analytical data, the product of the Willgerodt reaction with propionylmesitylene was assigned structure VI, N-(α-mesitoylthioacetyl)-morpholine. The compound VI appears to exist largely in the enolic form VIa and/or VIb. The ultraviolet spectrum which is shown in Fig. 1 consists of a single broad intense band with a maximum at 290 mμ (ϵ 17,000) and this is to be compared with the spectrum of N-(α-phenylthioacetyl)-morpholine, also shown in Fig. 1, which shows a sharp band at 279 mμ (ϵ 14,100) and a shoulder at 365 mμ (ϵ 230). For further comparison, the spectrum of N-(mesitoylthioformyl)-morpholine is shown in Fig. 2. This latter compound displays three maxima which are at 258 mμ (ϵ 8000), 314 mμ (ϵ 5900) and 407 mμ (ϵ 540). The bathochromic shift of 11 mμ found with VI can be accounted for on the basis of either structure VIa or VIb. The infrared spectrum of VI, however, gives evidence that perhaps VIa is the preferred form. There are weak absorptions in the 4μ region which are characteristic of S–H stretching[9] while in the 3μ region there are no bands characteristic of O–H stretching. A strong band appears at 6.29 μ and could be due to chelated unsaturated ketone structure[9] as is present in VIa. In the 6.7–6.9 μ region there are two bands which are characteristic of a thioamide grouping[9] and which are found in the spectra of all of the thioamides in this study. If this grouping was conjugated with a double bond, as in VIb, these bands would be expected to be shifted to longer wave length.



V VI

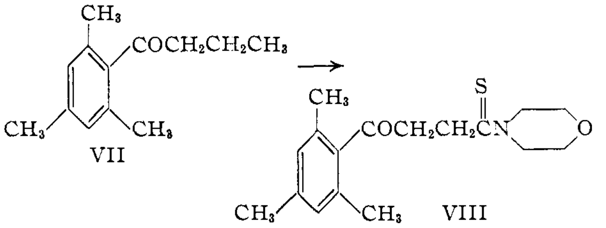


VIa



VIb

Although remote, the possibility exists that the formation of VI could have been due to enolization of propionylmesitylene followed by oxidation at the ω- or allylic carbon. Thus, n-butyrylmesitylene (VII) also was subjected to the Willgerodt reaction and the expected N-(β-mesitoylthiopropionyl)-morpholine (VIII) was isolated.



VII VIII

The ultraviolet spectrum of VIII is shown in Fig. 2, and it is seen that the 279 mμ (ϵ 13,500) band, characteristic of the thiomorpholide grouping, is present. Therefore, it appears that the products resulting from these three acylmesitylenes are, indeed, due to a Willgerodt type reaction.

The fact that acetyl-, propionyl- and n-butyrylmesitylene upon reaction with sulfur and morpholine under Willgerodt conditions yield a thioamide which retains the original carbonyl group instead of the usual des-keto thioamide can only be interpreted to mean that attack at the carbonyl group is not a necessary step in the reaction. Instead, the carbonyl group would appear to serve only to activate the α-carbon, and it is on this carbon atom the reaction begins. Other evidence consistent with this view is available from the results obtained by Por-

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[9] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

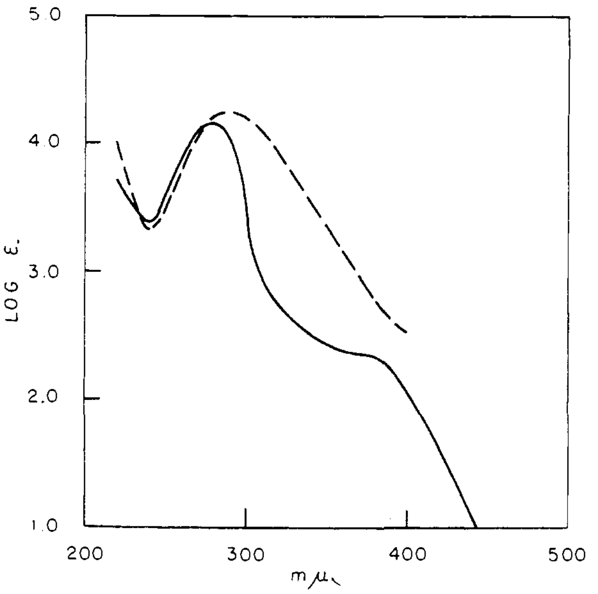


Fig. 1.—N-(α-Phenylthioacetyl)-morpholine, —; N-(α-mesitoylthioacetyl)-morpholine, ------.

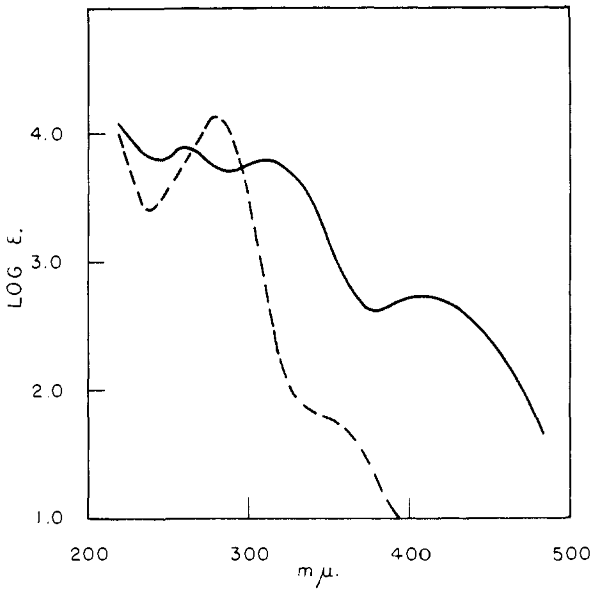
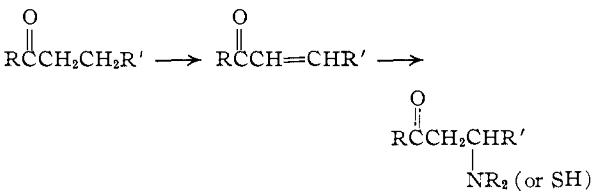


Fig. 2.—N-(Mesitoylthioformyl)-morpholine, —; N-(β-mesitoylthiopropionyl)-morpholine, -----.

ter,[10] who studied the reaction of alkylpyridines with sulfur and amines. It is known that an α- or γ-alkylpyridine behaves similarly to an alkyl ketone in that the pyridine nucleus activates the adjacent methylene group. Reaction of α- and γ-alkylpyridines with an amine and sulfur yields ω-thioamides or compounds derived from them, whereas β-alkylpyridines are recovered unchanged.

Whether this initial attack on the methylene alpha to the carbonyl is common to the Willgerodt reaction with both hindered and unhindered ketones is not known, but at the present time there appears to be no need for separate mechanisms for the two classes of compounds. At any time subsequent to the initial attack at the α-carbon, the carbonyl group of the unhindered ketone could be reduced to a methylene group. That such a reduction is possible is to be seen in the fact that the formation of a saturated hydrocarbon sometimes is a side reaction in the Willgerodt reaction.[11,12] It is unlikely that H_2S alone can be the reducing agent, since it is known to react with ketones to form *gem*-dithiols[13] and with β-keto-esters to yield β-thioketo-esters.[14]

In light of the present results, it is reasonable to propose that the initial intermediate in the reaction is not an olefin, as postulated by King and McMillan,[7] but rather an α,β-unsaturated ketone. Such an intermediate could be formed by attack on the α-carbon by sulfur followed by loss of H_2S. This olefinic linkage could then migrate down the chain, as suggested by King and McMillan,[7] by reversible additions and eliminations of an amine or H_2S to the olefinic bond. When a terminal double bond is formed, it is irreversibly oxidized to an acid derivative. If these steps be involved, the Willgerodt reaction on a methyl ketone could occur only by direct oxidation of the methyl group followed by reduction of the carbonyl group. It is to be realized, however, that as the number of different types of



$$R\overset{O}{\overset{\|}{C}}CH_2CH_2R' \longrightarrow R\overset{O}{\overset{\|}{C}}CH{=}CHR' \longrightarrow R\overset{O}{\overset{\|}{C}}CH_2\underset{NR_2\text{ (or SH)}}{\underset{|}{C}}HR'$$

compounds which undergo reaction with sulfur and an amine increases, the concept of a *single* mechanism for the Willgerodt reaction becomes meaningless.

Experimental[15]

Willgerodt Reaction with Acetylmesitylene.—A mixture of 2.00 g. (12.3 mmoles, b.p. 121.5–123.0°, $n^{25}D$ 1.5153) of acetylmesitylene, 0.40 g. (12.3 mmoles) of sulfur and 1.08 g. (12.3 mmoles) of morpholine was heated under reflux for 8 hr. The dark reaction mixture was cooled, poured into water and extracted with benzene. The benzene extract was washed with water and the solvent removed on the steam-bath under reduced pressure. The residue was dissolved in a mixture of 70-30 hexane–benzene and chromatographed on 20 g. of Merck alumina. Elution with 70-30 hexane–benzene afforded 0.87 g. (43.5%) of unreacted acetylmesitylene. Continued elution with the same solvent mixture yielded, after recrystallization from hexane, 0.71 g. (20.8%) of N-(mesitoylthioformyl)-morpholine (I) as orange-yellow needles, m.p. 99.2–101.1°.

An analytical sample was obtained by rechromatography on alumina and recrystallization from methanol–water, m.p. 101.0–101.5°.

Anal. Calcd. for $C_{15}H_{19}O_2NS$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 64.69; H, 7.08; N, 5.12; S, 11.61.

When the above reaction was performed except that 3 equivalents of sulfur were employed, the yield of thiomorpholide was increased to 33.5%, but the purification of the product was more difficult due to the presence of unreacted sulfur.

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[10] H. D. Porter, THIS JOURNAL, **76**, 127 (1954).

[11] L. F. Fieser and G. W. Kilmer, *ibid.*, **62**, 1354 (1940).

[12] C. Willgerodt, *Ber.*, **21**, 534 (1888).

[13] T. L. Cairns, G. L. Evans, A. W. Larchar and B. C. McKusick, THIS JOURNAL, **74**, 3982 (1952).

[14] S. K. Mitra, *J. Indian Chem. Soc.*, **15**, 31 (1938).

[15] Analyses were performed by the Microanalytical Laboratory, Department of Chemistry and Chemical Engineering, University of California. All melting points are corrected.

Alkaline Hydrolysis of N-(Mesitoylthioformyl)-morpholine (I).—A solution of 200 ml. of 95% ethanol, 10 ml. of 1 *N* NaOH solution and 2.50 g. (9.03 mmoles) of N-(mesitoylthioformyl)-morpholine was heated under reflux for 2 days, after which an additional 10 ml. of 1 *N* NaOH solution was added and the refluxing continued for one day longer. The condenser was removed and the ethanol distilled. When the residue was acidified with dilute HCl, H_2S was evolved. The acidic mixture was extracted with ether, the ethereal solution washed with water and then extracted with dilute NaOH.

The alkaline aqueous layer was acidified, extracted with ether, the ethereal solution washed with water, dried over $MgSO_4$ and the ether removed on a steam-bath. The residue (1.31 g.) was a dark oil which solidified on standing. Recrystallization from hexane–benzene yielded 1.05 g. (60.5%) of mesitylglyoxylic acid (II) as pale yellow, hard, dense crystals, m.p. 118.8–119.4° (lit.[16] 116°), mixed m.p. with authentic mesitylglyoxylic acid (m.p. 116.7–117.9°), was 117.9–119.3°. The infrared spectra of the two samples in $CHCl_3$ were identical.

Anal. Calcd. for $C_{11}H_{12}O_3$: neut. equiv., 192.2. Found: neut. equiv., 191.5.

The ether solution containing the neutral fraction was washed with water and dried over $MgSO_4$. The ether was removed on the steam-bath and the residual solid recrystallized from hexane, yield 508 mg. (21.5%), m.p. 127.8–128.5°, mixed m.p. with authentic N-(mesitoylformyl)-morpholine (III) (128.6–129.7°) was 128.8–129.6°. The infrared spectra of the two samples in CS_2 were identical.

An analytical sample was obtained by chromatography over alumina followed by recrystallization from hexane, m.p. 129.1–129.7°. The ultraviolet spectrum in 95% ethanol exhibited a maximum at 276 mμ (ε 8180) with rising end absorption toward 220 mμ.

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.95; H, 7.01; N, 5.14.

Mesitylglyoxylic Acid.[16]—With stirring, 2.00 g. (12.6 mmoles) of $KMnO_4$ dissolved in 40 ml. of water was added dropwise over a period of 30 minutes to a mixture of 1.00 g. (6.17 mmoles) of acetylmesitylene and 10 ml. of 2% NaOH solution. On continued stirring, the temperature of the reaction mixture rose to 40° and at that time the reaction was cooled in a cold water-bath. After a total of 2.5 hours of stirring, the reaction mixture was filtered through Super-Cel and the filtrate extracted with ether. Acidification of the alkaline filtrate gave an oil that was dissolved in ether, the ether layer washed with water, dried over $MgSO_4$ and the ether evaporated. Most of the oily residue solidified on standing in the cold. The entire residue was triturated with hot hexane–benzene and a small amount of white insoluble solid would not dissolve. The extract, on cooling, deposited 492 mg. (41.5%) of mesitylglyoxylic acid as a yellow solid, m.p. 115.0–117.5°. Two recrystallizations from benzene–hexane gave 320 mg. of material, m.p. 116.7–117.9° (lit.[16] 116°).

N-(Mesitoylformyl)-morpholine (III).—A mixture of 100 mg. (0.52 mmole) of mesitylglyoxylic acid, 1 drop of pyridine and 0.5 ml. (6.9 mmoles) of purified thionyl chloride was heated at 50° for 45 minutes. The excess thionyl chloride was removed under reduced pressure and the cooled residue treated with 0.50 g. (5.8 mmoles) of morpholine. After the exothermic reaction had subsided, the reaction mixture was heated on the steam-bath for ten minutes, cooled and water added. The solid was filtered and recrystallized from hexane to yield 111 mg. (81.6%) of the acylated morpholine, m.p. 128.6–129.7°.

Desulfurization of N-(Mesitoylthioformyl)-morpholine (I).—A mixture of 2.50 g. (9.02 mmoles) of N-mesitoylthioformyl)-morpholine, 250 ml. of ethanol and approximately 80 ml. of washed commercial Raney nickel was heated under reflux with vigorous stirring for 7 hr. The pale green solution was decanted and then filtered through Super-Cel. The residual Raney nickel was washed three times with hot ethanol and the washings filtered. The solvent from the combined ethanolic solutions was removed on the steam-bath and the residue dissolved in hexane. Attempts to extract this solution with dilute HCl solution resulted in the formation of considerable white solid which was filtered, yield 0.68 g. (26.4%). Recrystallization of the solid from ethanol–benzene yielded two crops of material. The first crop amounted to 268 mg., m.p. 201–210° dec., and the second crop to 356 mg., m.p. 201.0–201.6° dec. Recrystallization of the second crop gave 306 mg. of material, m.p. 202.1–202.4° dec., mixed m.p. with authentic α-mesityl-β-(N-morpholino)-ethanol hydrochloride (m.p. 200.5–201.7° dec.), 201.0–201.8° dec.

Anal. Calcd. for $C_{15}H_{32}O_2N \cdot HCl \cdot H_2O$: neut. equiv., 304. Found: neut. equiv., 306.

The aqueous acidic layer from the filtration of the extraction was basified with NaOH solution and the curdy precipitate which formed was extracted with hexane. The hexane was removed on the steam-bath and the residual yellow oil (0.62 g., 27.6%) which solidified on standing was recrystallized from aqueous methanol to yield 430 mg. of material, m.p. 85.8–86.5°. Recrystallization from aqueous methanol gave 344 mg. of α-mesityl-β-(N-morpholino)-ethanol (IV), m.p. 85.7–86.5°, mixed m.p. with authentic material, 85.5–86.3°. The infrared spectra of the two samples in CS_2 were identical.

ω-(N-Morpholino)-acetylmesitylene.—While cooling in an ice-bath, 5.0 g. (31 mmoles) of bromine was added to a stirred solution of 5.0 g. (30.9 mmoles) of acetylmesitylene in 20 ml. of glacial acetic acid over a period of 20 minutes. The reaction mixture (no bromine color) was poured into 50 ml. of cold water and extracted with hexane. The hexane extract was washed three times with water, dried over magnesium sulfate and the solvent removed on the steam-bath to yield 8.0 g. (of crude ω-bromoacetylmesitylene).

A solution of the crude bromo-ketone, 10.0 g. (115 mmoles) of morpholine and 50 ml. of anhydrous benzene was heated under reflux for 10 hr. The reaction mixture, containing solid material, was poured into water and the aqueous layer separated. An attempt to extract the organic layer with dilute acid resulted in the formation of a solid which was filtered. The crude hydrochloride was recrystallized from aqueous ethanol to yield 3.13 g. (33.5%) of ω-(N-morpholino)-acetyl mesitylene hydrochloride monohydrate, m.p. 252–254° (sintering 225°) dec. The analytical sample was dried at 115° and 0.5 mm. for 24 hr.

Anal. Calcd. for $C_{15}H_{21}O_2N \cdot HCl \cdot H_2O$: C, 59.69; H, 8.01; N, 4.64; neut. equiv., 302. Found: C, 59.86; H, 8.16; N, 4.74; neut. equiv., 301.

The aqueous layer from the two phase filtrate was basified with NaOH and the oil extracted with ether. After drying over $MgSO_4$, the ether was evaporated. The residual oil (1.40 g.) could not be induced to crystallize and so it was converted into the hydrochloride, m.p. 248–251° dec.

α-Mesityl-β-(N-morpholino)-ethanol (IV).—A mixture of 470 mg. (1.55 mmoles) of ω-(N-morpholinoacetylmesitylene) hydrochloride monohydrate, dilute NaOH solution and benzene was shaken until all the solid had disappeared. The benzene layer was dried over $MgSO_4$ and the solvent evaporated on the steam-bath. The residue was dissolved in 25 ml. of anhydrous ether and 0.25 g. (6.7 mmoles) of crushed $LiAlH_4$ was added in small portions, with stirring. Stirring was continued for 2 hr., and the excess hydride was decomposed with a mixture of ethanol–benzene. Water was added and the organic layer separated from the pasty solid. The solid was washed with a portion of ether and the ethereal solutions combined. After washing the ethereal solution with water, the solvent was removed on the steam-bath. The residual oil crystallized on standing and was recrystallized from aqueous methanol, yield 242 mg. (62.3%), m.p. 85.5–86.2°.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.31; H, 9.39; N, 5.69.

The hydrochloride prepared from this material had a m.p. 200.5–201.7° (dec.).

Willgerodt Reaction with Propionylmesitylene.—A mixture of 3.0 g. (17 mmoles, b.p. 132–134° (19 mm.), $n^{25}D$ 1.5095) of propionylmesitylene,[17] 1.09 g. (34 mmoles) of sulfur and 1.74 g. (20 mmoles) of morpholine was heated under reflux for 9 hr. The dark reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with saturated sodium chloride solution and the ether removed on the steam-bath. The residue was dissolved in 50–50 hexane–benzene and chromatographed on 50 g. of alumina. Elution with 200 ml. of 50–50 hexane–benzene yielded 1.07 g. (35.7%) of propionylmesitylene.

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[16] M. L. Van Scherpenzeel, *Rec. trav. chim.*, **19**, 379 (1900).

[17] A. Klages, *Ber.*, **35**, 2245 (1902).

Continued elution with the same solvent mixture gave 1.48 g. (29.8%) of crude N-(α-mesitoylthioacetyl)-morpholine (VI). Recrystallization, first from hexane and then from aqueous methanol, yielded 1.21 g., m.p. 128.8–130.4°.

Anal. Calcd. for $C_{16}H_{21}O_2NS$: C, 65.94; H, 7.26; N, 4.81; S, 11.01. Found: C, 66.06; H, 7.17; N, 4.97; S, 10.79.

The material from another experiment has a m.p. 121.0–123.6° after recrystallization from hexane. The two different melting forms are dimorphic crystals since their infrared spectra in $CHCl_3$ were identical. The compound gave an intense red color with aqueous methanolic $FeCl_3$ and was soluble in 5% aqueous sodium hydroxide and recovered upon acidification.

Acid Hydrolysis of N-(α-Mesitoylthioacetyl)-morpholine (VI).—A mixture of 185 mg. (0.64 mmole) of N-(α-mesitoylthioacetyl)-morpholine, 5 ml. of 6 *N* hydrochloric acid and 5 ml. of acetic acid was heated under reflux for 6 hr., during which time hydrogen sulfide was evolved. The reaction mixture was cooled, diluted with water and extracted with ether. The extract was washed with 5% sodium hydroxide (acidification of which yielded no material), saturated NaCl solution and dried over $MgSO_4$. The ether was removed on a steam-bath and the residue was an oil. This material was nitrated at 0° with fuming HNO_3.[18] The reaction mixture was swirled in the ice-bath for 30 seconds and then diluted with ice-water. The white precipitate was filtered and recrystallized from aqueous ethanol to yield 72 mg. (45%) of material, m.p. 136.5–138.5°. A mixed m.p. with an authentic sample of *dinitroacetylmesitylene* (m.p. 138.5–140.2°) was 137.5–138.8°. The infrared spectra of the two solid derivatives in $CHCl_3$ solution were identical.

Willgerodt Reaction with *n*-Butyrylmesitylene.—A mixture of 2.0 g. (10.5 mmoles, b.p. 145–147° (20 mm.), $n^{25}D$ 1.5049) of *n*-butyrylmesitylene,[17] 0.67 g. (21 mmoles) of sulfur and 1.80 g. (20.7 mmoles) of morpholine was heated under reflux for 7 hr. The reaction mixture was diluted with benzene, washed twice with water and then with saturated NaCl solution. The benzene was removed on the steam-bath and the residual oil dissolved in a mixture of 75–25 hexane–benzene and chromatographed on 25 g. of alumina. Elution with 50–50 hexane–benzene first yielded 1.13 g. of starting ketone and then 700 mg. of material which solidified on standing. The crude N-(β-mesitoylthiopropionyl)-morpholine was recrystallized three times from benzene–hexane, yield 285 mg. (8.8%), m.p. 99.7–100.4°.

Anal. Calcd. for $C_{17}H_{23}O_2NS$: C, 66.86; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.78; H, 7.32; N, 4.87; S, 10.41.

The low recovery yield from the recrystallizations was due to the extreme difficulty in obtaining colorless rather than slightly discolored crystals.

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[18] R. C. Fuson and J. T. Walker, THIS JOURNAL, **52**, 3269 (1930).

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE]

The Aconite Alkaloids. XXX.[1] Products from the Mild Permanganate Oxidation of Atisine[1,2]

BY S. WILLIAM PELLETIER AND WALTER A. JACOBS

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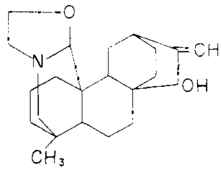
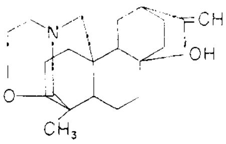
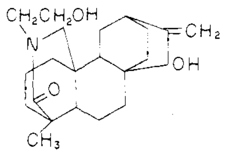
The structures assigned earlier to atisine (I) and isoatisine (II) are given additional support by further oxidation studies. Thus mild permanganate oxidation of atisine gave the γ-lactam, α-oxoatisine (VIIa), the δ-lactam, β-oxoatisine (VIIIa), and an unsaturated base (XI) in which the oxyethyl group of atisine is lacking. Catalytic reduction of β-oxatisine in 70% acetic acid gave the known dihydroöxoisoatisine (IX), thus relating oxidation products from the atisine and isoatisine series. Selective oxidation of α- and β-oxoatisine with a periodic acid–permanganate mixture afforded the corresponding dicarboxylic acids X and VI. A mixture of these acids was also isolated from the acidic fraction obtained from the mild permanganate oxidation of atisine. Vigorous permanganate oxidation of atisine in the presence of pyridine and sodium hydroxide gave a mixture from which only the δ-lactam dicarboxylic acid (VI) could be isolated. The transformations described interrelate the various degradation products of atisine and place the structures assigned to atisine and isoatisine on a firmer basis.



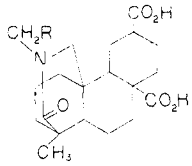
I



II



III



IV, R = CH_2OH
V, R = CO_2H

In recent communications on the Aconite Alkaloids, it has been shown that the various reactions of atisine[3] and isoatisine may be accounted for on the basis of structures I and II, respectively.[1,4,5] Mild permanganate oxidation of isoatisine in acetone and acetic acid furnishes a good yield of oxoisoatisine, $C_{22}H_{33}NO_3$,[6] III (*vide infra*), while more vigorous conditions give rise to an oxoisoatisinedicarboxylic acid[7] and an oxoisoatisinetricarboxylic acid[8] which will be shown to have structures IV and V, respectively. Although oxidation of atisine under vigorous conditions has given an analogous oxoatisinedicarboxylic acid

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[1] For paper XXIX in this series, see S. W. Pelletier and W. A. Jacobs, *Chem. and Ind.*, 1385 (1955).

[2] Presented in part at the Gordon Research Conference on Steroids and Related Natural Products, New Hampton, N. H., August 21, 1955.

[3] E. S. Stern, The Aconitum and Delphinium Alkaloids in "The Alkaloids, Chemistry and Physiology," edited by R. H. F. Manske and H. L. Holmes, Vol. IV, Academic Press, Inc., New York, N. Y., 1954, p. 280.

[4] K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chemistry and Industry*, 132 (1954); K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955). These workers were the first to propose the presently accepted carbon skeleton for the atisine alkaloids.

[5] S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **76**, 1496 (1954).

[6] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **170**, 515 (1947).

[7] W. A. Jacobs, *J. Org. Chem.*, **16**, 1593 (1951).

[8] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **174**, 1001 (1948).