

The Structure of MARQUIS' Nitroacetin

NIELS CLAUSON-KAAS and JØRGEN FAKSTORP

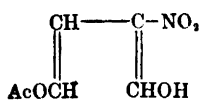
Chemical Laboratory of the University, Copenhagen, Denmark

In a paper by Rinkes¹ the fairly well known rules of nitration in the furan series have been reviewed. According to these rules, substitution, if possible at all, takes place in α -position. Even if both α -positions are occupied, the nitro-group is capable of removing other groups, *e. g.* carboxylic acid groups and sulphonic acid groups. If both α -positions are occupied with irreplaceable groups, β -substitution may in some cases take place. The only occurrence of β -nitration of a furan derivative with a replaceable α -group is the nitration of 5-methylfuroic acid which yields a small amount of 4-nitro-5-methylfuroic acid together with the expected 2-nitro-5-methylfuran².

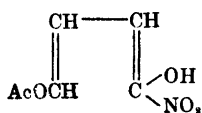
It has been shown, especially by the investigations of Marquis, Gilman, Rinkes and Johnson, that α -nitration of the furans in some cases proceeds through an intermediate addition product. Freure and Johnson³ have suggested that this is *always* the fact, but that the preliminary addition product usually has not been isolated because of its instability. There is much experimental evidence in favour of this theory and we also believe it to be true.

Several structures have been proposed for the addition products. This can be exemplified by nitroacetin, the addition product, formed when furan is nitrated in acetic anhydride at -5°C . This compound has been written as follows (I—V).

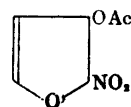
The formula I, originally proposed by Marquis⁴, was altered into II by Rinkes⁵ and by Gilman and Wright⁶ because nitroacetin when treated with



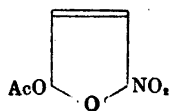
I



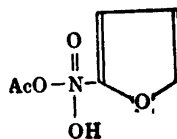
II



III



IV



V

pyridine yields α -nitrofuran. The formulas III and IV, advocating 1,2- and 1,4-addition, are due to Freure and Johnson. V is set forth by Gilman and Wright. Several oxonium formulas have also been proposed (see Gilman and Wright).

The oxonium formulas are incompatible with the solubility properties of nitroacetin. Therefore only the formulas II—V have to be taken into consideration. From a discussion given by Freure and Johnson in their paper it is evident that either formula III or formula IV is the correct one. Accordingly nitroacetin is formed by addition of the radicals $-\text{NO}_2$ and $-\text{OOC}\cdot\text{CH}_3$, presumably formed by the cleavage of a mixed anhydride of nitric acid and acetic acid (*cf.* Michael⁷) to furan. Freure and Johnson did not take any final decision between the two formulas, but seem to be inclined to IV⁸.

Already Marquis, who first synthesized nitroacetin, observed that it was easily hydrolyzed to malealdehyde, nitrous acid, and acetic acid. It seems strange to us, that this formation of malealdehyde has never been used as a decisive proof of the structure of nitroacetin, as the formation of this aldehyde, in our opinion, can only be explained by formula IV.

Hydrolysis of I should lead to malaldehyde (2-hydroxy-1,4-butanedial), II should yield succinic acid aldehyde, III malaldehyde and V succinic acid aldehyde.

We find the formation of malealdehyde by the hydrolysis of nitroacetin an unequivocal proof that the formula IV must be ascribed to nitroacetin.

Meanwhile Wohl and Mylo⁹ prepared malealdehyde starting from acetylene, and these authors obtained a bis-phenylhydrazone and a dioxime with melting-points entirely different from those reported by Marquis. Wohl and Mylo suggested that Marquis' compounds might be derivatives of fumaraldehyde, in spite of the fact, that Marquis prepared pyridazine by treating nitroacetin with hydrazine. It is evident, that pyridazine can only be derived from the *cis*-form of butenedial, malealdehyde, and not from the *trans*-form, fumaraldehyde. If therefore the suggestion of Wohl and Mylo is correct, a *cis-trans*-rearrangement of primary formed malealdehyde must have taken place during the formation of the two derivatives first mentioned, but not during the formation of pyridazine.

We have prepared several derivatives of malealdehyde, synthesized according to Wohl and Mylo. Of these only the bis-phenylhydrazone, the bis-methylphenylhydrazone and the bis-diphenylhydrazone were suitable for characterization by melting points, crystallographic properties and solubility. We have demonstrated all three products to be identical with the corresponding compounds obtained by hydrolysis of nitroacetin.

As to the bis-phenylhydrazone, the only one of the above named derivatives hitherto prepared, we found the melting point 171° on the Kofler stage, $180-184^{\circ}$ in a tube. Wohl and Mylo report $198-199^{\circ}$ (tube), Marquis $236-237^{\circ}$ (bloc Maquenne). In spite of several preparations we never isolated any compounds melting higher than 171° (Kofler). The difference between our melting point and the one reported by Wohl and Mylo may be due to an experimental error, but the melting point of Marquis' compound is so high, that his product must have been an isomer of malealdehyde-bisphenylhydrazone. It is of course impossible to deduce the structure of this isomer without further experiments.

All other properties of our product were in agreement with those found by Marquis and by Wohl and Mylo.

The identification of malealdehyde proves that the formula for nitroacetin is the formula IV of Freure and Johnson. We believe, that an analogous structure must be ascribed to all similar addition-products. α -Nitration of furans thus proceeds through a 1,4-addition, followed by a 1,4-elimination of acetic acid. This mechanism of the nitration process corresponds to the mode of action earlier discussed for α -substitutions in the furan series^{3, 6, 10}. Cf. also Shephard and Johnson¹¹.

The hydrolytical method employed here to prove the structure of nitroacetin is very convenient because of the ease, with which the carbonyl compounds formed by the reaction may be identified. We propose that the method should find general application in investigations on the constitution of similar 2,5-dihydrofurans.

EXPERIMENTAL

Hydrazones from malealdehyde tetraethylacetal

Malealdehyde tetraethylacetal was obtained from acetylene according to the method of Wohl and Mylo (*l. c.*) (b. p. $132-133^{\circ}/16$ mm). For preparation of the hydrazones, about 200 mg of acetal were boiled with 3 ml 0.01 *N* sulfuric acid and 2 ml of alcohol for 45 seconds. After cooling, a solution of the corresponding hydrazine in diluted acetic acid (12 ml) was added. The hydrazones precipitated immediately. The mixture was allowed to stand for some hours, then the precipitate was filtered off, washed thoroughly with water and dried *in vacuo* over calcium chloride. The yields of the crude hydrazones amounted to about 80 %.

Bis-phenylhydrazone. The crude product was dissolved in boiling acetone (solubility 5.3 g in 100 ml). An equal amount of benzene was added and the solution evaporated rapidly under atmospheric pressure until a large crop of crystals had settled. After cooling the precipitate was filtered off and washed with benzene. Yield of recrystallized proportionate to crude product 70 %. Yellow plates, m. p. 171° (Kofler stage), 180° (tube)*.

Ebullioscopic molecular weight determination in acetone with the Rieche apparatus.

$C_{16}H_{16}N_4$	Calc.	C 72.75	H 6.06	N 21.21	Mol. wt. 264
	Found	» 72.56	» 6.14	» 20.95	» » 273

Bis-methylphenylhydrazone. The crude product was recrystallized from acetone-benzene. Yield of recrystallized proportionate to crude product 50 %. This hydrazone is more soluble in benzene than is the bis-phenylhydrazone and it is better to recrystallize from acetone-alcohol as described below for the derivative prepared from nitroacetin. Yellow plates, m. p. 173° (Kofler stage and tube).

$C_{18}H_{20}N_4$ (292)	Calc.	C 73.97	H 6.85	N 19.18
	Found	» 73.50	» 6.85	» 18.87

Bis-diphenylhydrazone. This hydrazone is still more soluble in benzene than the former and can only be recrystallized from acetone-benzene in a 30 % yield. The crystals contain crystal-benzene which is removed by drying *in vacuo* over paraffin. A good yield (80 %) is obtained by recrystallizing from acetone-alcohol, and this product holds no crystal-alcohol. Yellow plates, m. p. 177° (Kofler stage), 180° (tube).

$C_{28}H_{24}N_4$ (416)	Calc.	C 80.77	H 5.77	N 13.46
	Found	» 80.07	» 5.80	» 13.41

Hydrazones from nitroacetin

Nitroacetin was prepared from 2.2 g of furan following Marquis' directions (*l. c.*). The yellow oil was transferred to a 25 ml volumetric flask which was filled with methanol to the mark.

Bis-phenylhydrazone. 5 ml of the methanolic solution of nitroacetin was diluted with methanol (50 ml), water (50 ml), and acetic acid (10 ml). 3.2 g of phenylhydrazine was added, and the mixture boiled for several minutes. After addition of another 50 ml of water, boiling was continued for about half a minute, and the mixture allowed to stand over night. The precipitate was filtered off, washed with water and dried *in vacuo* over calcium chloride. Yield 32 % proportionate to furan (Marquis reports 21 %). The crude product was recrystallized 3 times from acetone-benzene as described above. Yield of recrystallized to crude product 61 %. Yellow plates, m. p. 170° (Kofler stage), 184° (tube).

$C_{16}H_{16}N_4$ (264)	Calc. N 21.21	Found N 21.26
-------------------------	---------------	---------------

* All melting-points are corrected.

A careful crystallographic investigation in polarized light showed that the substance was in every respect identical with the hydrazone prepared from malealdehyde tetraethylacetal.

The boiling point of a saturated solution of one of the hydrazones in acetone was not altered by the addition of the other hydrazone. The bis-phenylhydrazone was prepared several times under various conditions including those described by Marquis, but no product melting higher than 171° could be isolated.

Bis-methylphenylhydrazone. Prepared in the same manner as the phenyl derivative. Yield of crude product 37 %. Recrystallization from acetone-alcohol. Yield of recrystallized to crude product 78 %. Yellow plates, m. p. 176° (Kofler stage and tube).

$C_{18}H_{20}N_4$ (292) Calc. N 19.18 Found N 19.06

Bis-diphenylhydrazone. Prepared as the phenyl derivate, yield 28 %. Recrystallized from acetone-alcohol. Yield of recrystallized to crude product 75 %. Yellow plates, m. p. 173—177° (Kofler stage), 179° (tube).

$C_{28}H_{24}N_4$ (416) Calc. N 13.46 Found N 13.67

The bis-methylphenylhydrazone and the bis-diphenylhydrazone exhibited properties in every respect identical with those found for the corresponding derivatives prepared from malealdehyde tetraethylacetal.

SUMMARY

The formula of Marquis' nitroacetin, the nitroacetate prepared by the action of nitric acid on furan in acetic anhydride, is established with certainty by identification of the malealdehyde formed when nitroacetin is hydrolyzed. This formula is identical with one of two alternatives proposed earlier by Freure and Johnson. The mechanism of α -nitration in the furan series is discussed. The hydrolytical method employed is recommended for general application.

All analyses have been made in the most careful way by our colleague Mr. O. Rosenlund Hansen.

During the investigation we have received financial aid from *Tuborg Fondet* (N. Clauson-Kaas) and *Det teknisk-videnskabelige Forskningsraad* (J. Fakstorp).

We wish to thank the director of the Chemical Laboratory of the University of Copenhagen, Professor Dr. A. Langseth, for his kind interest in our work.

REFERENCES

1. Rinkes, I. J. *Rec. trav. chim.* **51** (1932) 349.
2. Rinkes, I. J. *Rec. trav. chim.* **49** (1930) 1118.
3. Freure, B. T. and Johnson, J. R. *J. Am. Chem. Soc.* **53** (1931) 1142.

4. Marquis, R. *Ann. chim. phys.* (8) 4 (1905) 196.
5. Rinkes, I. J. *Rec. trav. chim.* 49 (1930) 1169.
6. Gilman, H. and Wright, G. F. *Chem. Rev.* 11 (1932) 323.
7. Michael, A. and Weiner, N. *J. Am. Chem. Soc.* 58 (1936) 294.
8. *L. c.*, 1147 (*cf.*, however, *id. ibid.* 1144).
9. Wohl, A. and Mylo, B. *Ber.* 45 (1912) 322; 45 (1912) 1746; *cf.* Wohl, A. and Bernreuther, E. *Ann.* 481 (1930) 1.
10. Klopp, A. H. and Wright, G. F. *J. Org. Chem.* 4 (1939) 142.
11. Shepard, A. F. and Johnson, J. R. *J. Am. Chem. Soc.* 45 (1923) 4385.

Received February 21, 1947.