6-Dimethylamino-4-(*p*-chlorophenyl)-4-(*p*-chlorobenzyl)-heptanone-3 (XII) was prepared by the same procedure as described for VII. From 15.2 g. (0.042 mole) of 2-(*p*-chlorophenyl)-2-(*p*-chlorobenzyl)-4-dimethylaminopentane nitrile was obtained 5.3 g. (32%) of an oily residue which analyzed correctly for the desired amino ketone.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO$: Cl, 18.11; N, 3.57. Found: Cl, 18.03; N, 3.49.

The **hydrochloride** was prepared in a similar manner as described for VIII. From 4.0 g. of 6-dimethylamino-4-(*p*-chlorophenyl)-4-(*p*-chlorobenzyl)-heptanone-3 was obtained 1.1 g. (26%); m. p. 56–58°.

Anal. Calcd. for $C_{22}H_{28}Cl_3NO$: Cl, 24.76; N, 3.27. Found: Cl, 24.54; N, 3.13.

Acknowledgment.—The nitrogen and chloride determinations were carried out in our Analytical Laboratory by Mr. E. W. Post.

Summary

The chloro analogs of methadone, 6-dimethylamino-4,4-bis-(*p*-chlorophenyl)-heptanone-3 and the 6-dimethylamino-4-(*p*-chlorophenyl-4-(*p*-chlorobenzyl)-heptanone-3 were prepared.

The hydrochlorides of these compounds showed no appreciable analgesic activity.

BELLEVILLE 9, NEW JERSEY RECEIVED JANUARY 29, 1949

[CONTRIBUTION FROM THE ORGANIC CHEMICAL INSTITUTE OF THE HUNGARIAN UNIVERSITY, "BOLYAI" OF RUMANIA]

Studies on Furan Compounds. II. Conversion of 2-Aceto-benzofuran to 2-Methyl-3-hydroxychromone

BY L. VARGHA, J. RAMONCZAI AND J. BÁTHORY

As is supposed, sugars represent the primary assimilation products in the vegetable kingdom, which then change under biological conditions to other important compounds. Our knowledge about the nature and intermediates of these manifold transformations is still very incomplete. It is probable that certain labile tautomeric forms of sugars, *e. g.*, furanoses, play an important part in these reactions. Since furanoses are closely related to true furan derivatives and since sugars easily give rise *in vitro* to furan derivatives, it may be assumed that eventually some of these biochemical transformations might proceed intermediately through furan compounds. In order to test this possibility, we have set as an object of our experiments the study of those transformations, which principally might take place also under biological conditions.

It was demonstrated by previous work[1] that the action of alcohols upon the *p*-toluenesulfonyl derivative of 2-acetofuranoxime results in the production of ammonium *p*-toluenesulfonate and an acetal of an unsaturated diketoaldehyde (hexen-2-dion-4,5-acetal-1). It was further shown that the corresponding saturated acetal (hexanedion-4,5-acetal-1) will be converted by acid hydrolysis to pyrocatechol, a substance which occurs in the vegetable kingdom.

The present contribution reports analogous researches, carried out on the *p*-toluenesulfonyl derivative of 2-acetobenzofuranoxime (I) in methanolic and ethanolic medium, respectively. From the methanolic reaction product, in addition to ammonium *p*-toluenesulfonate (II), three substances of entirely differing properties could be isolated. Two of them ($C_{10}H_8O_3$ and $C_8H_6O_2$) were colorless crystalline substances, the third was an almost colorless liquid ($C_{12}H_{14}O_4$) distillable *in vacuo* without decomposition. The ethanolic reaction product yielded the same crystalline substances, and in addition a liquid ($C_{14}H_{18}O_4$) having properties very similar to those of the oily compound $C_{12}H_{14}O_4$.

The constitution of the crystalline products have been established. They were found to represent 2-methyl-3-hydroxychromone (VII), a hitherto unknown substance closely related to flavonol, and 2-coumaranon[2] (*o*-hydroxyphenylacetolactone (XI)), respectively.

The correctness of the structure VII rests on the following experimental facts. The compound is very stable toward heat and acids, but decomposes on boiling with alkalies, giving rise to salicylic acid. Oxidation with hydrogen peroxide yields also salicylic acid, in addition to carbon dioxide. The formation of salicylic acid is in accordance with the chromone structure, the positive iodoform test indicates an $-O-C-CH_3$ group. The presence of a carbonyl group could not be demonstrated by the usual reagents as in the case of many other chromone and γ-pyrone derivatives. Attempts to prepare oxonium salts remained unsuccessful, too. The presence of one acidic hydroxyl group has been proved by determination of the active hydrogen, by the deep violet-blue color reaction with ferric chloride and by the formation of alkali salts and monoacyl derivatives. The fact that VII gives the corresponding methyl ether with diazomethane only in the presence of methanol, indicates, according to newer investigations by Schönberg and Mustafa,[3] a hydrogen bridge structure (VIIc). It is probable that the absence of the oxonium salt formation is partly due also to the chelate structure VIIc.

(1) Vargha, Ramonczai and Bite, THIS JOURNAL, **70**, 371 (1948).

(2) Stoermer, *Ann.*, **313**, 84 (1900).

(3) Schönberg and Mustafa, *J. Chem. Soc.*, 746 (1946).

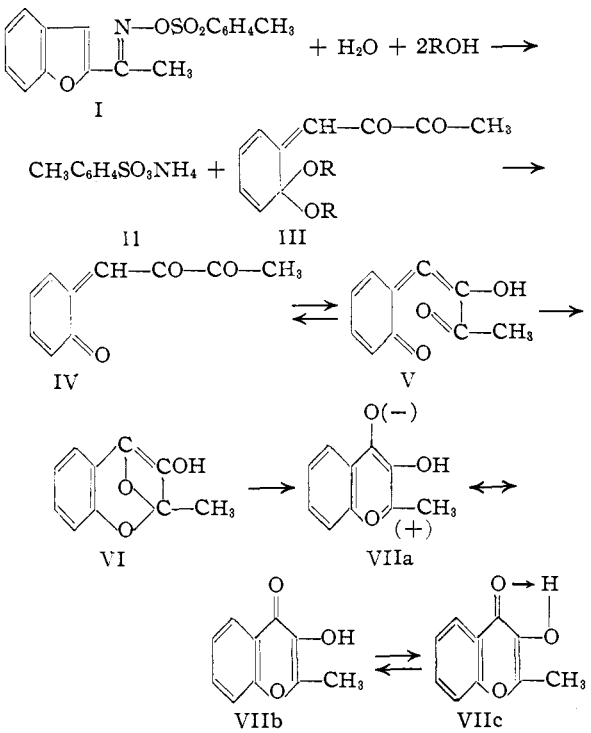
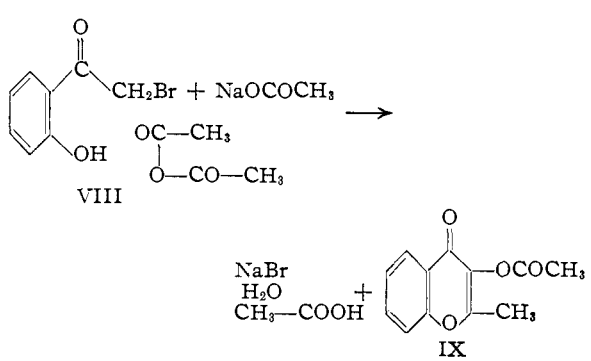


Fig. 1.—R = CH_3 or C_2H_5.

Though VII has been already mentioned in a publication by Wittig,[4] we could find neither the properties nor the method of preparation of this substance in the literature. Therefore, in order to prove definitely the structure VII, we synthesized it, through its acetate (IX) from *o*-hydroxy-ω-bromoacetophenone (VIII), acetic anhydride and sodium acetate, following a method,[4] which is generally applicable in the preparation of chromone derivatives



The 2-methyl-3-acetoxychromone (IX), prepared in this way, and the 2-methyl-3-hydroxychromone, obtained by hydrolysis of the acetate IX, proved to be identical with the acetate of VII and VII itself, respectively. Consequently the structure formula VII can be regarded as correct.

(4) Wittig, *Ann.*, **446**, 156 (1926).

A possible explanation for the transformation of I to VII is represented by Fig. 1. The elementary formula of VII and the fact that the reaction between I and alcohols gives rise to II in almost quantitative yield make it probable that the formation of VII, in the first phases, takes place in an anologous way as in the uncondensed furan series.[1] The resulting unstable *o*-quinonoid acetal (III) rearranges then with migration of an oxygen atom to VII.

The second crystalline reaction product (XI) cannot be separated from the liquid one by distillation, but it crystallizes gradually from the distillate. A quantitative separation of these products may be achieved by extraction of an ether solution of the distillate with sodium hydroxide, which takes up only XI. After acidification of the alkaline solution *o*-hydroxyphenylacetic acid[5] was isolated. This fact and the formation of *o*-hydroxyphenylacetanilide[2] and phenylhydrazide,[2] respectively, demonstrates sufficiently the correctness of structure XI. It may be supposed that the formation of 2-coumaranone (XI) from I proceeds in an analogous way to the conversion of the *p*-toluenesulfonyl derivatives of certain aromatic ketoximes in the presence of alcohols. Such compounds undergo, according to investigations by Neber, *et al.*,[6] first a Beckman rearrangement, then the intermediate suffers hydrolytic cleavage with the formation of an amine (Fig. 2).

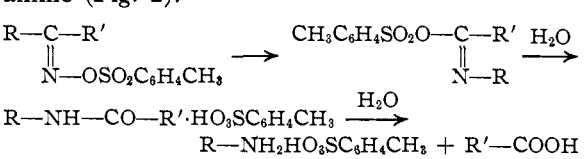
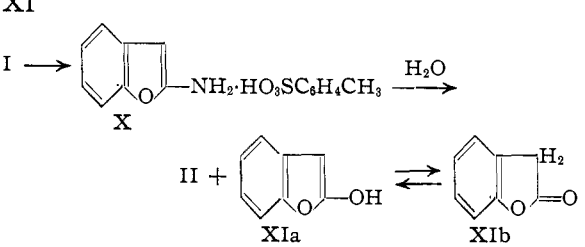


Fig. 2.

According to Fig. 2, 2-aminobenzofuran *p*-toluenesulfonate (X) should arise from I, which then, owing to its instability, is hydrolyzed to XI

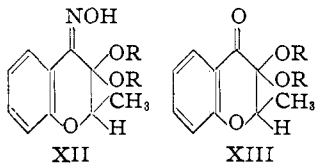


The constitution of the liquid reaction products could not be completely elucidated. These substances yield easily with hydroxylamine two different oximes, which can be smoothly converted by acid hydrolysis to VII. Based upon this fact and the analytic results, the oximes represent probably 2 - methyl - chromanone - 4 - oxime - 2-dimethylacetal and diethylacetal, respectively,

(5) Czaplicky, v. Kostanecki and Lampe, *Ber.*, **42**, 828 (1909).

(6) Neber and Friedolfsheim, *Ann.*, **449**, 109 (1926); Neber and Huh, *ibid.* **515**, 292 (1935).

(XII, R = CH_3 and C_2H_5). Hence the liquids should have the structure XIII.



XII XIII (R = CH_3 or C_2H_5)

This acetal structure, however, does not explain either the stability of the liquids toward acids or the fact that they do not yield, by cleavage of alcohol with quinoline and benzoyl chloride according to Claisen's method,[7] 2-methyl-3-hydroxychromone (VII).

Experimental

2-Acetobenzofuranoxime[8] was prepared from the corresponding ketone[9] in alcoholic solution and recrystallized from benzene; yield, 80%; m. p. 154–155°.

p-Toluenesulfonyl 2-Acetobenzofuranoxime, I.—Forty-two grams of powdered *p*-toluenesulfonyl chloride was added gradually to a solution of 2-acetobenzofuranoxime (35 g.) in 80 cc. of pyridine at 0° with stirring. After being kept at 0° for two hours the reaction mixture was poured into ice water. The white crystalline precipitate was filtered off, washed with water and dried *in vacuo* over calcium chloride; yield, almost quantitative; m. p., 100–102°. The substance can be recrystallized cautiously from a little hot benzene without decomposition. It also can be prepared readily by adding *p*-toluenesulfonyl chloride to an ethereal suspension of the sodium derivative of the oxime.

Anal. Calcd. for $C_{17}H_{15}O_4NS$: C, 61.97; H, 4.59; N, 4.24. Found: C, 62.33; H, 4.64; N, 4.16.

2-Methyl-3-hydroxychromone, VII.—A suspension of 50 g. of the *p*-toluenesulfonyl derivative I in 250 cc. of methanol was kept at 35° with occasional shaking for seven days. Then, after standing at 0° overnight, the precipitated mixture of ammonium *p*-toluenesulfonate and VII was filtered off. The filtrate was concentrated *in vacuo* to a small volume, to which 200 cc. of ether was added. After standing in a refrigerator for twelve hours the precipitate was filtered again. The combined solids were treated with 200 cc. of water and the insoluble part was filtered, dried and recrystallized from alcohol or benzene; yield, 9.2 g., 35%; m. p., 184–185°. From the aqueous filtrate 22 g. (76%) of ammonium *p*-toluenesulfonate was obtained after evaporation to dryness. 2-Methyl-3-hydroxychromone crystallizes in colorless prisms and gives in aqueous-alcoholic solution with ferric chloride a deep blue-violet coloration. According to the Zerewitinow method, the substance contains one atom of active hydrogen.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.16; H, 4.58; mol. wt., 176. Found: C, 68.14; H, 4.75; mol. wt., 175.5, by Rast's method, in camphor.

The substance was recovered unchanged after boiling in alcoholic medium with hydroxylamine, phenylhydrazine and semicarbazide, respectively, and did not give an oxonium salt either with hydrochloric acid or with zinc chloride. It produced, with iodine and potassium hydroxide, iodoform (m. p., 119°), and remained unchanged after refluxing with 2 *N* hydrochloric acid for two hours. It is soluble in warm diluted sodium or potassium hydroxide solution with yellow color, and the formed alkali salts precipitate on cooling in yellow crystals, from which the starting material can be recovered by acids.

Anal. Calcd. for $C_{10}H_7O_3Na$: Na, 11.61. Found: Na, 11.63.

(7) Claisen, *Ber.* **40**, 3908 (1907).
(8) Vongerichten, *ibid.*, **34**, 775 (1901).
(9) Stoermer, *ibid.*, **36**, 2863 (1903).

2-Coumaranone (*o*-Hydroxyphenylaceto Lactone, XI).—The ethereal mother liquor of the previous preparation was washed with water and dried by anhydrous sodium sulfate. After evaporation of the solvent the remaining oil distilled at 88–98° (2 mm.). From this distillate 2-coumaranone[2] crystallized gradually, m. p. 52°, after recrystallization from petroleum ether (b. p., 30–50°). The substance yielded, when heated with equimolecular amounts of aniline or phenylhydrazine in a little petroleum ether (b. p. 70–80°) on the water-bath, the anilide[6] (m. p. 155°), respectively, the phenylhydrazide[6] (m. p. 184°) of the *o*-hydroxyphenylacetic acid.

Anal. Calcd. for the anilide, $C_{14}H_{13}O_2N$: C, 73.99; H, 5.76. Found: C, 73.95; H, 5.67.

Anal. Calcd. for the phenylhydrazide, $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.82. Found: C, 69.68; H, 6.01.

2-Methylchromanone-3-dimethylacetal, XIII.—The ethereal mother liquor obtained from 50 g. of I was washed with water and shaken with 50 cc. of 2 *N* sodium hyroxide for one hour. The dried ether layer was evaporated and the residual liquid distilled *in vacuo;* b. p., 120–122° (4 mm.); yield, 6.8 g., 20.5%. The acetal is a faintly yellow, almost colorless liquid; it is readily soluble in the common organic solvents, insoluble in water.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.30; H, 6.10.

The acetal remained unchanged after boiling with 25% sulfuric acid for several hours and after heating with quinoline and benzoyl chloride at 130° for eight hours.[7] It is stable also toward 10% sodium hydroxide and was not attacked by hydrogen peroxide in glacial acetic acid solution after refluxing for four hours. In all these experiments the starting material was recovered in the form of its oxime.

The alkaline aqueous layer was acidified and filtered from some precipitated VII (1.2 g.). The filtrate was extracted with ether, the ether layer dried and evaporated to dryness. The residual *o*-hydroxyphenylacetic acid[5] was recrystallized from petroleum ether (b. p., 70–80°); yield 2 g., 20% (m. p. 147–149°).

Anal. Calcd. for $C_8H_8O_3$: C, 63.11; H, 5.30. Found: C, 63.30; H, 5.21.

2-Methylchromanone-3-diethylacetal, XIII.—The preparation of the diethylacetal was carried out in the same manner as that of the dimethylacetal, but ethanol was applied instead of methanol. The resulting liquid showed similar chemical behavior to the dimethylacetal; b. p. 118–122° (2 mm.).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.30. Found: C, 67.23; H, 7.17.

2-Methyl-3-acetoxychromone (IX) was prepared from VII with acetic anhydride in pyridine solution and recrystallized from 40% ethanol. The colorless needles melted at 111–112°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.03; H, 4.62; mol. wt., 218. Found: C, 66.35; H, 4.80; mol. wt., 218, by Rast's method, in camphor.

The *benzoate* of VII was prepared by the Schotten-Baumann method. The colorless crystals, obtained in almost quantitative yield, crystallized from ethanol, m. p. 165°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.86; H, 4.31. Found: C, 72.53; H, 4.37.

The *p-toluenesulfonate* was prepared in pyridine solution and recrystallized from acetone; yield, nearly quantitative; m. p. 152°.

Anal. Calcd. for $C_{17}H_{14}O_5S$: C, 61.79; H, 4.27. Found: C, 61.96; H, 4.54.

2-Methyl-3-methoxychromone, prepared from VII with diazomethane in ether–methanol (5:1) consisted of colorless needles which crystallized from dilute ethanol; m. p. 106°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.45; H, 5.29. Found: C, 69.41; H, 5.53.

Oxidation of VII by Hydrogen Peroxide.—One gram of VII in 10 cc. of glacial acetic acid was refluxed with 10 cc. of a 15% hydrogen peroxide solution for four hours in an apparatus which allowed the quantitative absorption of the evolved carbon dioxide by a barium hydroxide solution. After evaporation of the solvent *in vacuo* the solid reaction product was recrystallized from water. The colorless substance proved to be salicylic acid; m. p. and mixed m. p. with an authentic sample, 158°. The quantity of the evolved carbon dioxide was found to be nearly one equivalent.

Alkaline Cleavage of VII.—A solution of VII (3.4 g.) in 100 cc. of 2 *N* sodium hydroxide was refluxed for two hours. After acidification by 50% sulfuric acid the formed precipitate was filtered off and found to be salicylic acid; m. p. and mixed m. p. with an authentic sample, 158°.

***o*- and *p*-Hydroxy-ω-bromoacetophenone.**—These substances are repeatedly mentioned in the literature, but we could find a description neither of their preparation nor of their properties. We prepared them in manner similar to *o*-hydroxy-ω-chloroacetophenone,[10] as follows.

A mixture of powdered anhydrous aluminum chloride (40 g.) and phenyl bromoacetate[11] (20 g.) was heated at 135–140° for seven hours. The reaction product was decomposed by ice water, the insoluble solid filtered off, washed with water and dried. For separation of the *o*- and *p*-isomers, the dry mixture was extracted with boiling petroleum ether (b. p. 80–90°), in which only the *o*-isomer dissolved. After filtration and concentration of the filtrate, the *o*-hydroxybromoacetophenone (VIII) crystallized on cooling. It was recrystallized from petroleum ether (b. p., 80–90°) with charcoal, yield, 10 g.; m. p., 70–71°. The *p*-hydroxybromoacetophenone was recrystallized from alcohol; yield, 6 g.; m. p., 146°. Phenyl bromoacetate was prepared by heating an equivalent mixture of phenol and bromoacetyl bromide at 150–155° for five hours.

Anal. Calcd. for $C_8H_7O_2Br$: Br, 37.18. Found for the *o*-derivative: Br, 37.13; for the *p*-derivative: Br, 37.10.

Synthesis of 2-Methyl-3-acetoxy-chromone, IX, and 2-Methyl-3-hydroxychromone, VII.—A mixture of *o*-hydroxybromoacetophenone (1 g.), acetic anhydride (2 g.) and anhydrous sodium acetate (1 g.) was heated at 180° for ninety minutes. After treatment with water the formed substance was filtered off and recrystallized from petroleum ether (b. p. 80–90°); m. p. and mixed m. p. with the acetate of VII, 112°; yield, 0.6 g.

For hydrolysis the acetate (0.2 g.) was dissolved in 10 cc. of concd. sulfuric acid and to the colorless solution 100 cc. of water was added gradually with cooling by ice. The separated substance was filtered off, washed with water and recrystallized from alcohol. It has been found to be identical with VII; m. p. and mixed m. p. 184°.

2-Methylchromanoneoxime 3-Dimethylacetal, XII (R = CH_3) and its Benzoyl Derivative.—A mixture of the dimethylacetal (XIII, 2.2 g.), hydroxylamine hydrochloride (1 g.) and anhydrous sodium acetate (1 g.) in 25 cc. of alcohol was refluxed for four hours. After filtration and evaporation *in vacuo*, the oily residue soon became crystalline on stirring with water. It was obtained as white needles after recrystallization from 70% alcohol; m. p., 156–157°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.88; N, 5.90.

The benzoyl derivative of the oxime crystallized from ethanol, m. p. 140°. *Anal.* Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.11. Found: C, 66.91; H, 5.86; N, 4.23.

2-Methylchromanoneoxime-3-diethylacetal (XII, R = C_2H_5) crystallized from low boiling petroleum ether, m. p. 87–88°. It was easily soluble in common organic solvents. *Anal.* Calcd. for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.77; H, 7.27; N, 5.52.

The phenylhydrazone of XII (R = C_2H_5), prepared in aqueous solution buffered with sodium acetate, crystallized as colorless needles from 70% ethanol, m. p. 122°. *Anal.* Calcd. for $C_{20}H_{24}O_3N_2$: C, 70.56; H, 7.13; N, 8.23. Found: C, 70.34; H, 7.46; N, 8.50.

VII from XII.—A solution of either dimethyl or diethylacetal oxime (0.5 g.) was refluxed in 10 cc. of alcohol with 10 cc. of 2 *N* sulfuric acid for two hours. The substance, precipitated on cooling, was found to be 2-methyl-3-hydroxychromone; m. p. and mixed m. p. with an authentic sample, 184–185°.

Summary

On treating *p*-toluenesulfonyl 2-acetobenzofuranoxime (I) with methanol and ethanol, in addition to ammonium *p*-toluenesulfonate, four different substances were isolated. The identity of two of them has been definitely established as being 2-methyl-3-hydroxychromone (VII) and 2-coumaranone (XI), respectively. A probable explanation has been given as to the mechanism of formation.

The constitution of the two other products could not be quite definitely elucidated; they represent possibly 2-methyl-chromanone-3-dimethylacetal and diethylacetal (XIII), respectively.

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(10) Fries and Pfaffendorf, *Ber.*, **43**, 214 (1910).

(11) Kunckell and Scheven, *ibid.*, **31**, 172 (1898).