HETEROCYCLIZATION OF 1,5-DIKETONES BY CATALYTIC REDUCTION (REVIEW)

V. G. Kharchenko, N. S. Smirnova, V. N. Kravtsova, L. M. Yudovich, and A. D. Shebaldova

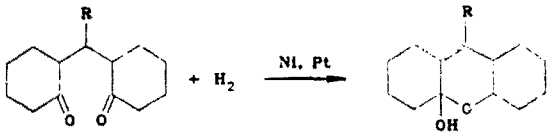
UDC 547.7/8'442.5.07: 542.941'541.128(047)

Literature reports and the writers' own work on the synthesis of saturated six-membered oxygen heterocycles by catalytic reduction of 1,5-diketones are reviewed.

Since heterocyclic compounds of the tetrahydropyran and dihydropyran series and their condensed analogs are structural components of naturally occurring compounds, they are of interest as model compounds in the chemistry of carbohydrates. There have also been patent reports of the use of compounds of this type in perfumery, and as bactericides, insecticides, fungicides, repellants, monomers, plasticizers, and solvents [1, 2].

One of the best methods of synthesis of tetrahydropyrans and related compounds is by reducing 1,5-diketones. The favorable relative dispositions of the carbonyl groups in 1,5-diketones, their tendency to undergo reversible cyclization under normal conditions by ring-chain tautomerism, and the availability of convenient methods for their preparation from readily available starting materials all favor the extensive use of such compounds for the preparation of saturated oxygen heterocycles [3-5].

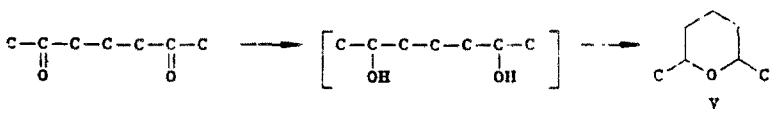
Until recently, only isolated examples of the reduction of 1,5-dicarbonyl compounds had been reported. The first such report was by Allwinn et al. [6]. The bicyclic 1,5-diketone (I) was reduced in the presence of skeletal nickel in methanol or with platinum black in ethanol to the 4*a*-hydroxydodecahydroxanthene (II).



I R=H II

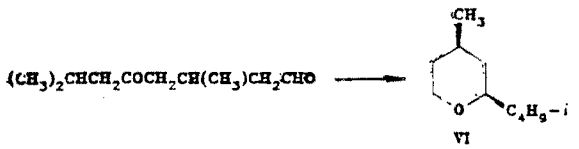
Further examination of this reaction showed that, in the presence of skeletal nickel, bicyclic diols were obtained [7]. The findings reported in [6] do not contradict those in [7], since the hemiacetal (II), as will be shown below, is an intermediate in the reductive cyclization of the methylenebiscyclohexanone (I) to the perhydroxanthene (III) and the diol (IV).

Hydrogenation of a straight-chain, 1,5-diketone over platinized charcoal gave the tetrahydropyran (V) [8], which these workers assumed to be formed by ring closure of the intermediate diol, although no evidence in support of this route was adduced.



V

2-Isobutyl-4-methyltetrahydropyran (VI) has been obtained by catalytic reduction of 3,7-dimethyl-5-oxooctanal over skeletal nickel at 125°C under a hydrogen pressure of 140 atm. [9]. The reaction was stereoselective, giving 90-95% of the cis-isomer:

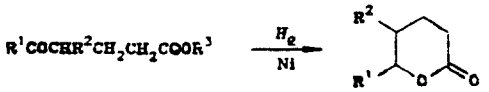


VI

N. G. Chernyshevskii Saratov State University, Saratov 110026. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1011-1018, August, 1990. Original article submitted April 5, 1989.

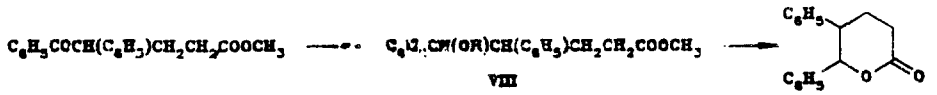
0009-3122/90/2608-0843$12.50

An example of the catalytic reduction of δ-keto acids to α-tetrahydropyranones (VII) has been reported [10]:



VII

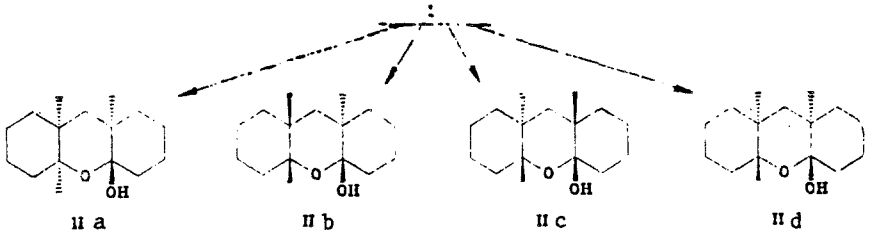
In the case of methyl 4,5-diphenyl-5-oxopentanoate, the intermediate alcohol (VIII) was isolated. This cyclized to the α-tetrahydropyrone on heating:



VIII

The reports most frequently encountered in the literature are those describing the catalytic reduction of the alkylidenecyclanones (I). These are known [4] to be able to exist in the hemiacetal form, the formation of which is favored by the conditions and a substituent in the 9-position, which stabilize the enol form. In many instances, the intermediate reduction products of 1,5-diketones (keto alcohols) also exist for the most part in the cyclic form [3]. All these properties favor the heterocyclization of 1,5-diketones on reduction.

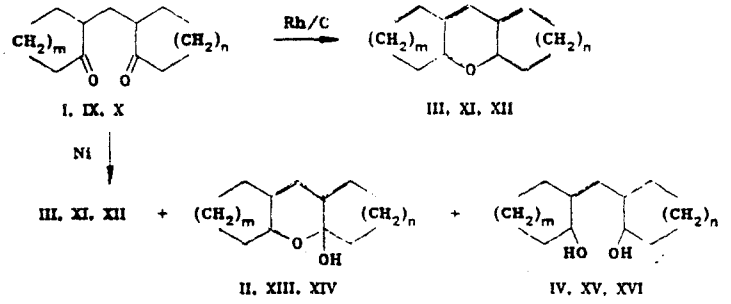
Reduction of 2,2'-methylenedicyclohexanone (I) over an Adams platinum catalyst has been reported [7, 11] to give 4*a*-hydroxydodecahydroxanthene (II). The hemiacetal (II) has four asymmetric carbon atoms. Of the eight possible diastereoisomers, four have so far been obtained and characterized. The cis-syn-trans isomer (IIa) was obtained by hydrogenating the erythro-diketone (I). threo-Diketone (I) gave the cis-anti-trans- and trans-anti-cis-isomers (IIb, c), while the hemiacetal with the trans-syn-trans configuration (IId) was obtained by reduction of both forms of the diketone (I) with sodium in ether [7]. In the latter case, epimerization occurred to give the more stable isomer.



II a II b II c II d

The availability of convenient methods for the synthesis of 1,5-diketones of varied structure [5] has allowed us [12-32] to carry out a systematic study of their heterocyclization by catalytic hydrogenation, and to establish the characteristic features of this reaction with respect to the catalyst, solvent, temperature, hydrogen pressure, and the structure of the diketone used.

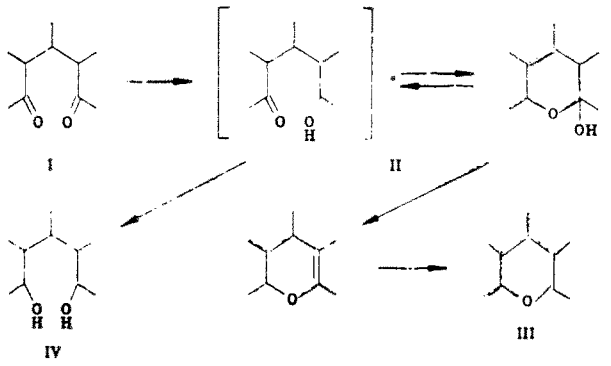
1,5-Diketones incorporating five- and six-membered rings (I, IX, X), in the presence of acidic, heterogeneous ruthenium and rhodium catalysts are converted into the corresponding tetrahydropyrans over a wide temperature range (20-120°C) at hydrogen pressures of 8.08-10.1 MPa {12-14, 16-19, 22]:



I—IV $m=n=2$; IX, XI, XIII, XV $m=2$, $n=1$; X, XII, XIV, XVI $m=n=1$

In the presence of skeletal nickel or a basic ruthenium catalyst, the nature and extent of the reactions of (I) vary greatly. For example, over nickel at low temperatures reduction of the carbonyl groups predominates, the principal product being the diol (IV). As the temperature is raised, the amounts of the perhydroxanthene (III) increase to 50%, the yields of the hemiacetal (II) decreasing accordingly. Separate experiments on the hydrogenation of the hemiacetal (II) and the diol (IV) have shown that the hemiacetal (II) is converted either into the perhydroxanthene (III) (over a rhodium catalyst), or the diol (IV), or

a mixture of (III) and (IV) (over skeletal nickel). The diol (IV) is resistant to further hydrogenation. These findings are in accordance with those reported in [7], and suggest the following scheme for the reduction of 1,5-diketones (I) [14]:

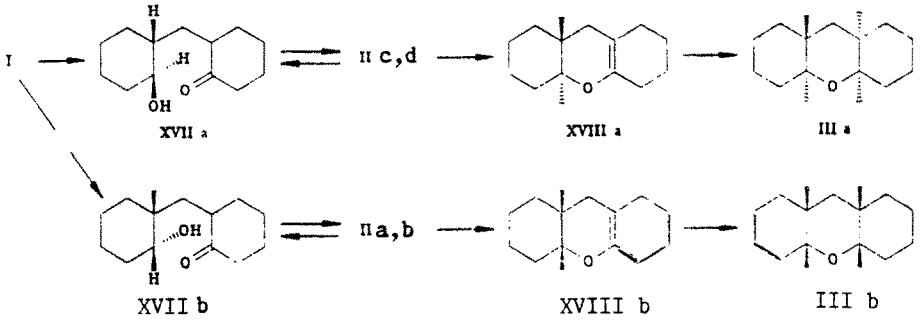


The formation of the tetrahydropyran (III) and the diol (IV) appears to take place concurrently via the intermediate keto alcohol or its cyclic form (II).

The above scheme provides an explanation for the temperature dependence of the reduction of the diketone (I) in the presence of, for example, skeletal nickel. As the temperature is raised, the rate of dehydration of the hemiacetal (II) increases, thereby increasing the proportion of the tetrahydropyran (III). The presence of an acidic catalyst (rhodium on charcoal) also facilitates the dehydration of the intermediate (II), resulting in the formation of quantitative yields of the perhydroxanthene (III) on hydrogenation of the methylenedicyclohexanone (I) even at ambient temperature.

The intermediate hemiacetal (II) isolated by us [14] is, according to its IR spectrum and melting point, identical to the cis-anti-trans-hemiacetal (IIb) [7]. Analysis of the reaction products of hydrogenation of the diketone (I) in the presence of a rhodium catalyst by ^{13}C NMR spectroscopy showed that the resulting perhydroxanthene is a mixture of the trans-anti-cis- and cis-syn-cis-isomers (IIIa, b) [30].

The stereochemistry of the reaction can be rationalized on the basis of the above reaction sequence. The structures of the perhydroxanthenes (IIIa) and (IIIb) are evidently determined by the structures of the oxo alcohols (XVIIa) and (XVIIb), formed in the first stage of the reaction:



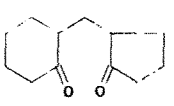
The initial reduction of one of the carbonyl groups afford oxo alcohols in which the hydroxyl groups are oriented axially (XVIIb), which under the hydrogenation conditions may isomerize to the equatorial alcohols (XVIIa). According to [3], (XVIIa) and (XVIIb) exist in the hemiacetal form (II), giving on dehydration, respectively, the trans- and cis-$\Delta^{4a,9a}$-decahydroxanthenes (XVIIIa, b), cis-hydrogenation of which affords the trans-anti-cis- and cis-syn-cis-perhydroxanthenes (IIIa, b):

It is important to note that, under the conditions examined, the stereochemical outcome of the reaction is virtually independent of the isomeric composition of (I). Hydrogenation of the pure threo-form and a mixture of the threo- and erythro-forms of the diketone affords identical mixtures of perhydroxanthenes, which may be rationalized in two ways: either at the dehydration stage the threo- and erythro-forms of the diketone (I) are converted into the same mixture of isomeric decahydroxanthenes (XVIIIa, b), or under these conditions an equilibrium is established between the two forms of the diketone.

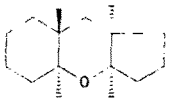
Equilibria between the cyclic and open-chain forms of 1,5-diketones are dependent on the pH of the medium [4]. A similar shift in the equilibrium for compounds (I), (IX), and (X) could explain the formation of diols on catalytic hydrogenation of diketones over skeletal nickel [17-19]. The small amounts of alkali present in this catalyst evidently stabilize the open-chain form of the intermediate hydroxyketone (XVII), hydrogenation of which gives the diols (IV), (XV), and (XVI).

The 1,5-diketone (X), which contains two five-membered rings, is more difficult to reduce than the diketones (I) and (IX) [14]. This difference appears to be due to the different rates of reduction of the cyclohexanone and cyclopentanone carbonyl groups. Examination of the hydrogenation products of the diketones (IX) and (X) by ^{13}C NMR showed the presence of two isomers, the configurations of which were identical with that proposed for the perhydroxanthene (III) [30].

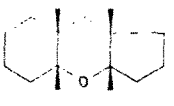
Hydrogenation of the 1,5-diketones (I) and (IX) affords cis-syn-cis- and trans-anti-cis-tetrahydropyrans in a ratio of 1:2, whereas hydrogenation of (X) gives a ratio of 1:6. This difference in isomer ratios could be due to the differing thermodynamic stabilities of the intermediate axial alcohols. For condensed derivatives of cyclohexanol, they are approximately the same. The relative stabilities of cyclopentanols with axially and equatorially oriented hydroxy-groups apparently differ to a lesser extent, which also results in a change in the stereoisomer ratios.



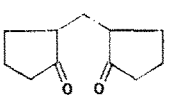
IX



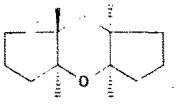
trans-anti-cis



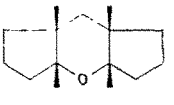
cis-syn-cis



X

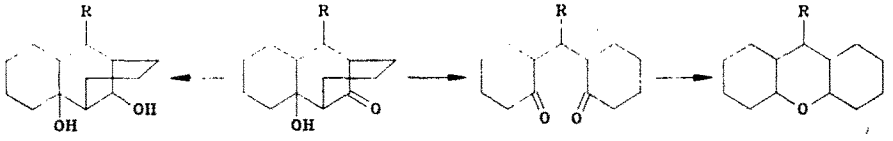


trans-anti-cis



cis-syn-cis

9-Substituted perhydroxyanthenes can be obtained from 8-substituted-2-hydroxytricyclo[7.3.1.$0^{2,7}$]tridecan-13-ones (XIX-XXI), which on catalytic hydrogenation undergo retroaldol cleavage to the corresponding 1,5-diketones (I, XXII, XXIII) [22, 30]. By selecting the reaction conditions, it is possible to direct this reaction toward the formation of perhydroxanthenes:

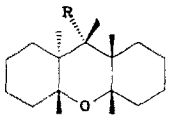


XXVI – XXVIII XIX – XXI I, XXII, XXIII III, XXIV, XXV

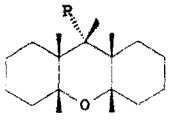
I, III, XIX, XXVI R=H; XX, XXII, XXIV, XXVII R=CH_3; XXI, XXIII R=C_6H_5; XXV, XXVIII R=C_6H_{11}

In some instances, in addition to cleavage of the cycloketones (XIX-XXI) followed by hydrogenation of the resulting 1,5-diketones (I), (XXII), and (XXIII), direct reduction of the carbonyl group occurs to give the tricyclic diols (XXVI-XXVIII) in yields of up to 15%.

According to ^{13}C NMR spectroscopy, the hydrogenation products of the ethylidenedicyclohexanone (XXII), formed by retroaldol cleavage of the cyclic ketol (XX), comprise a mixture of the 9β-methyl-trans-anti-cis- and 9β-methyl-cis-syn-cis-perhydroxanthenes (XXIVa, b):

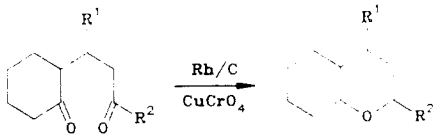


III a, XXIV a



III b, XXIVb, XXVb

The ability of 1,5-diketones to undergo heterocyclization on reduction is also exemplified by the hydrogenation of the semicyclic mono- and diaryl diketones (XXIX). However, as a result of steric hindrance due to the aryl substituents, the reduction of these compounds requires higher temperatures (120-150°C) than are required for the bicyclic 1,5-diketones (I, IX, X) [23, 25, 26]:

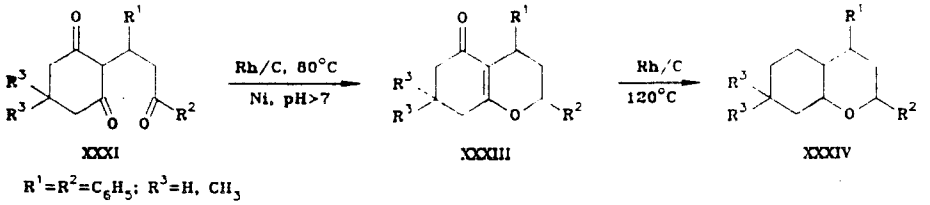


XXIX XXX

R^1=H, C_6H_5, 4-$CH_3OC_6H_4$; R^2=C_6H_5, 4-$CH_3OC_6H_4$

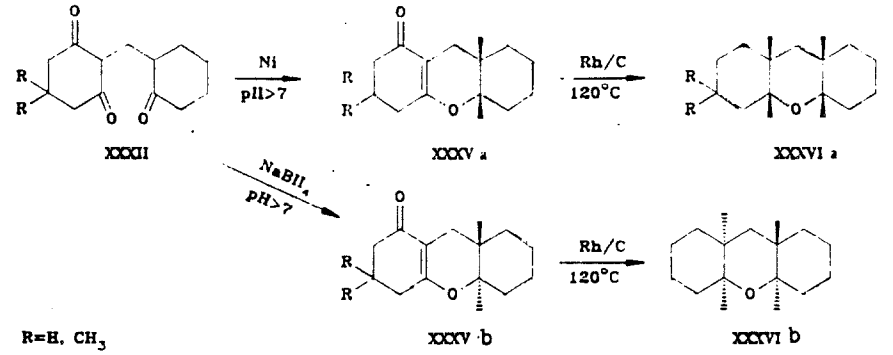
The presence of a methoxy group in the aryl substituents still further hinders the reduction of the diketones (XXIX), and their conversion into the tetrahydropyrans (XXX) proceeds in low yield at temperatures of at least 150°C. A rhodium catalyst, unlike a copper-chromium catalyst, facilitates reduction of the phenyl substituents to cyclohexyl. With diaryl-substituted diketones, depending on the reaction conditions, selective reduction of one or both aromatic rings occurs. In many instances, hydrogenolysis of the methoxy group takes place [23].

The catalytic reduction of semi- and bicyclic oxo-1,5-diketones (XXXI, XXXII) is of special interest, in that it affords the possibility of obtaining the intermediate dihydropyrans [12, 15, 16, 19-21, 23, 25, 26, 28, 29, 31]:



XXXI XXXIII XXXIV

R^1=R^2=C_6H_5; R^3=H, CH_3



XXXII XXXV a XXXVI a

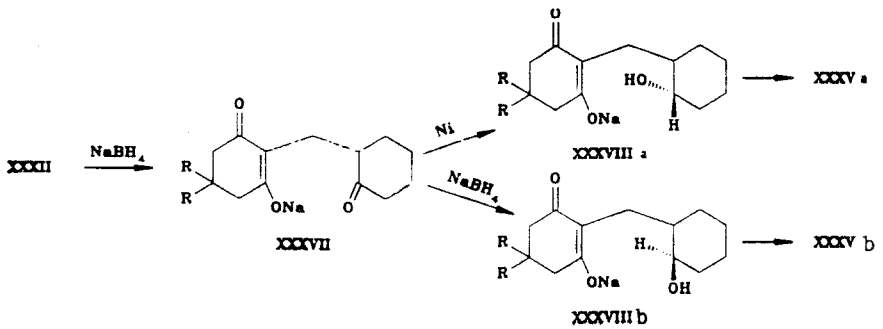
XXXV b XXXVI b

R=H, CH_3

Using a rhodium catalyst at 80°C and a hydrogen pressure of 10.1 MPa, or skeletal nickel in an alkaline medium, the oxo-1,5-diketones (XXXI and XXXII) are converted mainly into the 1-oxodecahydroxanthenes (XXXIII, XXXV). When the temperature is raised to 120°C, the dihydropyrans (XXXIII, XXXV) are reduced to tetrahydropyrans, the oxo-group not involved in cyclization being completely reduced to CH_2 (XXXIV, XXXVI).

The 1-oxodecahydroxanthenes (XXXIII, XXXV) can exist, depending on the mode of coupling of the carbo- and heterocycles, in two isomeric forms. According to our findings [29], oxohydroxanthenes obtained by reducing the oxo-1,5-diketones (XXXII) over skeletal nickel in an alkaline medium have the cis-configuration (XXXVa).

The trans-isomer of the oxohydroxanthene (XXXVb) is obtained on reducing the oxo-1,5-diketones (XXXII) with sodium borohydride. Since in both cases reduction takes place in an alkaline medium, the starting triketones (XXXII) exist in the open form (XXXVII), as shown by the signals for the carbon atoms of the free carbonyl groups in the ^{13}C NMR spectra:



XXXII XXXVII XXXVIII a XXXV a

XXXVIII b XXXV b

Treatment of the triketones (XXXII) with sodium borohydride results, as is usual in such cases, in axial attack of the hydride ion on the carbonyl group of the cyclohexane ring, giving the oxo-alcohols (XXXVIIIb) with an equatorial hydroxy group. Treatment of the latter with acid affords the trans-isomers of the oxohydroxanthenes (XXXVb).

Catalytic reduction of (XXXII) clearly affords the alcohols (XXXVIIIa) with an axially-oriented hydroxy group, leading to the formation of the cis-1-oxodecahydroxanthenes (XXXVa). Under more severe hydrogenation conditions, the axial alcohols (XXXVIIIa) isomerize to the more thermodynamically favored equatorial alcohols (XXXVIIIb), as shown by separate studies [29]. Consequently, the presence in the 1-oxodecahydroxanthenes (XXXV) of a fragment with a given configuration controls the stereochemistry of the perhydroxanthenes (XXXVI). Hydrogenation of the cis- and trans-isomers (XXXVa, b) results in the formation of the cis-syn-cis- and trans-anti-cis-perhydroxanthenes (XXXVIa, b).

From a consideration of the foregoing, it may be concluded that the catalytic reduction of 1,5-diketones is of special interest in the developing area of the chemistry of dicarbonyl compounds. Further developments in this area will obviously involve an examination of the mechanisms and stereochemistry of reactions of compounds of this type.

LITERATURE CITED

1. J. Dazzi, US Patent No. 2,949,473; *Chem. Abstr.*, **55**, P4531.
2. G. I. Brendel and L. H. Shepherd, US Patent No. 3,751,432; *Ref. Zh. Khim.*, N183P (1974).
3. R. É. Valter, *Ring-Chain Isomerism in Organic Chemistry* [in Russian], Zinatne, Riga (1987), p. 238.
4. V. I. Vysotskii, N. V. Vershinina, and M. N. Tilichenko, *Zh. Org. Khim.*, **9**, 2427 (1973).
5. V. G. Kharchenko and S. N. Chalaya, *1,5-Diketones* [in Russian], Izd. Saratov Un-ta, Saratov (1977), p. 85.
6. R. Allwinn, J. Colonge, R. Cviegel, and J. Dreux, *Bull. Soc. Chim. Fr.*, Nos. 8-9, 1178 (1958).
7. J. Mounet, J. Huet, and J. Dreux, *Bull. Soc. Chim. Fr.*, No. 8, 3006 (1971).
8. N. I. Shuikin and G. K. Vasilevskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 3, 557 (1964).
9. H. Davis, US Patent No. 3,394,169; *Ref. Zh. Khim.*, 16R513P (1969).
10. R. Bertocchio, R. Longeray, and J. Dreux, *Bull. Soc. Chim. Fr.*, No. 1, 60 (1964).
11. A. Palsky, J. Huet, and J. Dreux, *Bull. Soc. Chim. Fr.*, No. 12, 5003 (1968).
12. A. P. Kriven'ko, K. M. Korshunova, V. N. Kravtsova, L. I. Markova, N. N. Sorokina, A. A. Terekhin, O. V. Fedotova, V. G. Kharchenko, L. G. Chichenkova, A. D. Shebaldova, N. S. Smirnova, G. I. Rybina, L. V. Vlasova, A. F. Blinokhvatov, and S. N. Chalaya, *The Chemistry of Dicarbonyl Compounds*: Abstracts of Reports of the 4th All-Union Conference on the Occasion of the 95th Birthday of Gustav Vanag, Academician of the Academy of Sciences of the Latvian SSR, Riga (1976), p. 155.
13. V. G. Kharchenko, A. D. Shebaldova, V. N. Kravtsova, and A. A. Terekhin, USSR Author's Certificate, No. 559,922; *Byull. Izobret.*, No. 20, 5 (1977).
14. V. G. Kharchenko, V. N. Kravtsova, A. D. Shebaldova, and A. A. Terekhin, *Zh. Org. Khim.*, **15**, 1412 (1979).
15. V. G. Kharchenko, N. S. Smirnova, L. I. Markova, G. I. Rybina, and K. M. Korshunova, *Zh. Org. Khim.*, **15**, 1961 (1979).
16. V. G. Kharchenko, A. D. Shebaldova, V. N. Kravtsova, L. I. Markova, N. S. Smirnova, and A. A. Terekhin, in: 4th International Symp. on Heterogeneous Catalysis, Abstracts of Reports, Varna (1979), p. 415.
17. V. G. Kharchenko, A. D. Shebaldova, V. N. Kravtsova, and A. A. Terekhin, USSR Author's Certificate, No. 697,516; *Byull. Izobret.*, No. 42, 98 (1979).
18. V. G. Kharchenko, A. D. Shebaldova, V. N. Kravtsova, N. S. Smirnova, and A. F. Pronin, *Topics in the Chemistry of 1,5-Diketones and Compounds Derived Therefrom* [in Russian], Izd. Saratov Univ., Saratov (1979), p. 86.
19. A. D. Shebaldova, N. S. Smirnova, V. N. Kravtsova, L. I. Markova, and L. V. Vlasova, in: 7th International Symp. on the Chemistry of Heterocyclic Compounds, Abstracts of Reports, Bratislava (1981), p. 106.
20. V. G. Kharchenko, N. S. Smirnova, L. I. Markova, L. V. Vlasova, G. I. Rybina, and K. M. Korshunova, in: 3rd All-Union Symp. on Heterogeneous Catalysis and the Chemistry of Heterocyclic Compounds, Abstracts of Reports, Riga (1981), p. 62.
21. V. G. Kharchenko, N. S. Smirnova, A. P. Kriven'ko, O. V. Fedotova, T. G. Nikolaeva, and L. I. Markova, in: The Chemistry of Dicarbonyl Compounds: Abstracts of Reports of the 5th All-Union Conf. on the Occasion of the 100th Birthday of Academician of the Academy of Sciences of Latvian SSR Gustav Vanag [in Russian], Riga (1981).
22. V. G. Kharchenko, N. S. Smirnova, L. I. Markova, L. V. Vlasova, and A. A. Terekhin, *Zh. Org. Khim.*, **17**, 873 (1981).
23. V. G. Kharchenko, N. S. Smirnova, L. I. Markova, L. V. Vlasova, G. I. Rybina, and K. M. Korshunova, *Zh. Org. Khim.*, **18**, 804 (1982).

24. N. S. Smirnova, L. I. Markova, K. M. Korshunova, and G. I. Rybina, *Studies in the Synthesis and Catalysis of Organic Compounds* [in Russian], Izd. Saratov Univ., Saratov (1983), p. 208.
25. V. G. Kharchenko, N. S. Smirnova, L. I. Markova, G. I. Rybina, and K. M. Korshunova, USSR Author's Certificate, No. 910,633; *Byull. Izobret.*, No. 9, 86 (1982).
26.. V. G. Kharchenko, N. S. Smirnova, L. K. Kulikova, L. V. Vlasova, L. I. Markova, G. I. Rybina, and K. M. Korshunova, *Khim.-farm. Zh.*, No. 6, 688 (1983).
27. N. S. Smirnova, L. M. Yudovich, and G. I. Rybina, *Nucleophilic Reactions of Carbonyl Compounds*, Abstracts of Reports, All-Union Conference, Saratov (1985), p. 37.
28. N. S. Smirnova, L. M. Yudovich, G. I. Rybina, and L. I. Markova, *The Chemistry of Dicarbonyl Compounds*, Abstracts of Reports of the 6th All-Union Conference, Riga (1986), p. 204.
29. V. G. Kharchenko, N. S. Smirnova, L. M. Yudovich, G. I. Rybina, and L. I. Markova, *Zh. Org. Khim.*, **23**, 576 (1987).
30. V. G. Kharchenko, N. S. Smirnova, L. M. Yudovich, G. I. Rybina, and O. V. Bryukhanova, *Zh. Org. Khim.*, **23**, 2333 (1987).
31. N. S. Smirnova, V. G. Kharchenko, L. I. Markova, L. M. Yudovich, and G. I. Rybina, in: 4th All-Union Symposium on Heterogeneous Catalysis and the Chemistry of Heterocyclic Compounds, Abstracts of Reports, Riga (1987), p. 134.
32. V. G. Kharchenko, N. S. Smirnova, and A. P. Kriven'ko, in: 4th All-Union Symposium on Heterogeneous Catalysis and the Chemistry of Heterocyclic Compounds, Abstracts of Reports, Riga (1987), p. 30.

REACTIONS AT SURFACES.

3.* REACTIONS OF 3-METHYL-3-BUTEN-1-OL WITH CARBONYL COMPOUNDS ON METAL SALT SURFACES

U. G. Ibatullin, Yu. V. Pavlov, and M. G. Safarov

UDC 541.48:547.28'361'811

Condensation of 3-methyl-3-buten-1-ol with pentanal or acetone occurs on metal salt surfaces at room temperature to give di- and tetrahydropyrans.

We have reported [1] that the condensation of 3-methyl-3-buten-1-ol (I) with carbonyl compounds on solid carrier surfaces depends to a large extent on physical adsorption. The presence of a developed surface enables the molecules of the reactants to orient themselves appropriately, and to form a transitional complex which is converted into products. It could be that this reaction would occur even in the absence of such surfaces, if coordinating centers such as metal ions are present which are able to form sufficiently reactive intermediate complexes.

We have now examined the condensation of the alcohol (I) with pentanal (IIa) and acetone (IIb) at the surfaces of salts of mono-, di-, and trivalent metals. In addition to the change on the central atom, the anion, reactant, and salt (previously dehydrated) ratios were varied [2]. It is known [3] that water of crystallization is not directly bonded to the metal ion, but occupies free sites in the salt crystal lattice. By dehydrating the salts, access of the reactants to the central ion and complexation therewith were facilitated. All the experiments were carried out at ambient temperatures (Tables 1 and 2).

*For Communication 2, see [1].

Bashkir State University, Ufa 450074. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1019-1021, August, 1990. Original article submitted January 3, 1989; revision submitted May 3, 1989.

0009-3122/90/2608-0849$12.50