*Anal.* Calcd. for $C_{20}H_{16}O_2NCl$: C, 71.11; H, 4.74; N, 4.14; Cl, 10.51. Found: C, 70.50; H, 4.97; N, 3.81; Cl, 10.35.

*4-Benzoylbenzoic acid* (XV). Five grams of XIII was heated for 1 hr. in a solution of 1.8 g. of sodium hydroxide in 40 ml. of water. The acidification with hydrochloric acid gave 3 g. (91%) of XV which formed in ethanol gray leaflets, m.p. 191.5–192°. (Zincke[9] indicates the same melting point.)

*Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.42. Found: C, 73.96; H, 4.27.

*2-[(4'-Benzoyl)benzoyl)benzofuran* (XVI). A mixture of 4 g. of XIII, 2 g. of salicylaldehyde, and 2.2 g. of potassium carbonate in 50 ml. of acetone was refluxed with stirring for 10 hr. The mixture was poured into 250 ml. of water. The crystallized material was filtered off and recrystallized in an ethanol and dioxane (10%) mixture. Thus, 4.2 g. (84%) of XVI was obtained, yielding in pure dioxane creamy microcrystals, m.p. 162°. In sulfuric acid, this compound formed an orange yellow halochromic coloration.

*Anal.* Calcd. for $C_{22}H_{14}O_3$: C, 80.98; H, 4.17. Found: C, 80.98; H, 4.27.

IX formed bright colorless needles (from petroleum ether at low temperature) m.p. 58°.

*Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 76.84; H, 8.00.

*Acknowledgment.* We are indebted to Dr. J. L. Cuzin for his interest in this work and to S.E.I.T.A (Paris) for financial support of one of us (C. H.).

PARIS, FRANCE

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[CONTRIBUTION FROM THE AGRICULTURAL RESEARCH LABORATORY, ORGANIC CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

# Pyranylation of Amides

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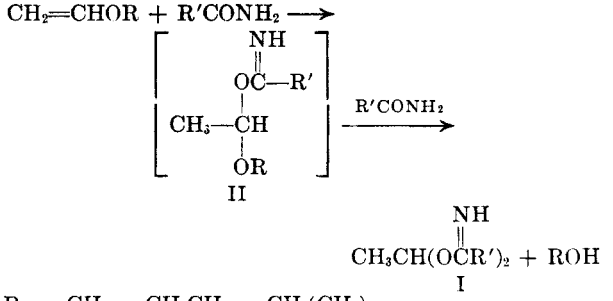
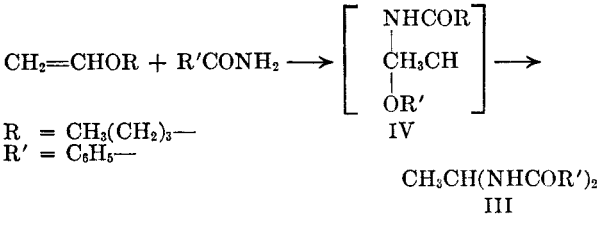
It has been found that 2,3-dihydropyran, in the presence of catalytic amounts of hydrogen chloride, forms 1:1 adducts with amides. The products of this reaction have been formulated as *N*-(2-tetrahydropyranyl)amides. Amides that undergo pyranylation include aromatic and aliphatic amides, ureas, sulfonamides, and imides.

Glacet[1,2] found that strongly basic amines (amylamine) do not add to 2,3-dihydropyran whereas aromatic amines (aniline, *N*-methylaniline) do.[3] After the completion of our work Robins and Lewis[4] reported the addition of purines to 2,3-dihydropyran and 2,3-dihydrofuran in the presence of an acid catalyst. This paper deals with the addition of amides, which are only very slightly basic, to 2,3-dihydropyran, a cyclic vinyl ether.

Addition of amides to vinyl ethers has been reported by Voronkov.[5] The products were reported to be ethylidene-*O*-acylamides (I). The mono-*O*-acylamide derivatives (II) were supposedly intermediates in this reaction.




Furukawa and co-workers[6] reported the addition of benzamide to phenyl vinyl ether and *n*-butyl vinyl ether. Ethylidenedibenzamide (III), the *N*-alkylated product, was obtained from these reactions. α-Butoxyethylbenzamide (IV) was suggested as the intermediate.




*p*-Toluenesulfonamide also gave the corresponding ethylidene di-*p*-toluenesulfonamide presumably *via* the α-amido ether intermediate. However, *N*-methyl-*p*-toluenesulfonamide reacted with *n*-butyl vinyl ether to give *N*-methyl-*N*-α-butoxyethyl-*p*-toluenesulfonamide. In this case the second molecule of amide did not replace the alkoxy group.

The reactions of vinyl ethers with acidic imino compounds such as dicarboxylic acid imides have been investigated.[6] These compounds added to vinyl ethers to give α-imido ethers (V). The products were shown to be *N*-alkylated by removal of alcohol from the α-imido ether to form known *N*-vinylimides (VI).

(1) C. Glacet, *Bull. soc. chim.*, 575 (1954).

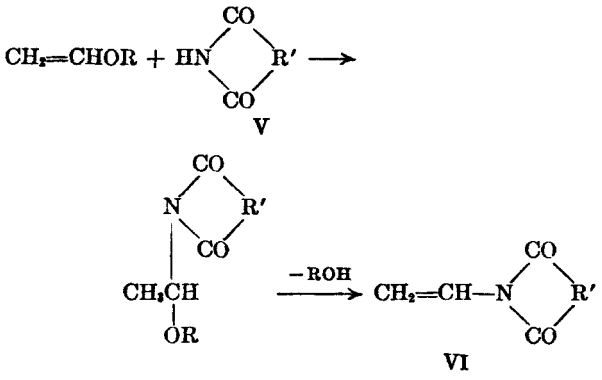
(2) C. Glacet and G. Bonnemaison, *Compt. rend.*, **247**, 305 (1958).

(3) The reaction of 2,3-dihydropyran with alcohols, acids, and mercaptans is well known; W. E. Parham and D. M. Delaitsch, *J. Am. Chem. Soc.*, **70**, 4187 (1948); W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **76**, 4962 (1954). H. D. Finch, E. A. Peterson, and S. A. Ballard, *J. Am. Chem. Soc.*, **74**, 2018 (1952).

(4) R. K. Robins and L. R. Lewis, 138th ACS National Meeting, Sept. 11–16, 1960, New York, N. Y.

(5) M. G. Voronkov, *J. Gen. Chem.* (*U.S.S.R.*), **21**, 1494 (1951).

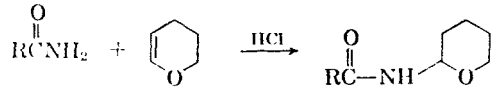
(6) J. Furukawa, A. Onishi, and T. Tsuruta, *J. Org. Chem.*, **23**, 672 (1958).



V VI

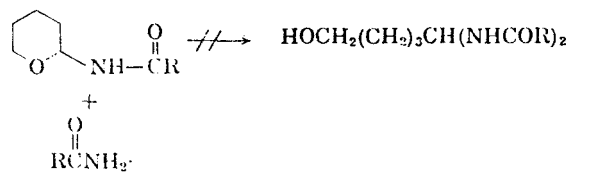
Thus, the literature dealing with alkylation of amides by alicyclic vinyl ethers is not conclusive with regard to the structure of the products. The pyranylation of amides with 2,3-dihydropyran has been shown in this laboratory to give *N*-(2-tetrahydropyranyl)amides (VII).

2,3-Dihydropyran, in the presence of catalytic amounts of hydrogen chloride, reacted with various amides in benzene-dimethylformamide solvents to form adducts upon several hours of heating at 80–90°. The use of dimethylformamide as a solvent greatly enhances the ease of reaction. It appears that this is due to the fact that homogeneous solutions are obtainable with this solvent.



VII

The structure of these adducts has been established on the basis of infrared analysis and hydrolysis experiments. All the products show C=O bands at 1655–1737 cm.$^{-1}$ One N-H stretching band instead of two and the absence of the amide II band of primary amides indicate a secondary amide structure for the adducts. A triplet band characteristic of tetrahydropyran structures (2-methoxytetrahydropyran—1075 cm.$^{-1}$, 1061 cm.$^{-1}$, and 1031 cm.$^{-1}$) is exhibited by the adducts. 2,3-Dihydropyran exhibits peaks at 1067 cm.$^{-1}$ and 1050 cm.$^{-1}$ No bands were found which could be assigned to alcohols. These elements of the infrared spectra refute the possible ring opening which could conceivably occur with the introduction of a second amide molecule.



Attempted hydrolysis of the benzamide-dihydropyran adduct with dilute alcoholic sodium hydroxide over a fifty-seven-hour period gave a 74% recovery of starting material. Compounds of structure VII would be expected to exhibit stability in basic solution.[7,8] Imino esters, the products expected from *O*-alkylation, should hydrolyze readily to esters.[9,10] The inability of the adducts to form hydrochloride salts, infrared analysis, and negative hydrolysis experiments eliminate imino esters from consideration.

Hydrolysis of *N*-(2-tetrahydropyranyl)benzamide with concentrated phosphoric acid gave benzamide and 5-hydroxyvaleraldehyde. The aldehyde was isolated as its 2,4-dinitrophenylhydrazone. Acid hydrolysis of this $\alpha$-substituted tetrahydropyran would be expected to give these products.[2,6,11] The mechanism of hydrolysis is probably similar to acetal hydrolysis.[12] An alternate path of reaction may involve prior elimination of benzamide and subsequent hydrolysis of 2,3-dihydropyran since under the conditions used 2,3-dihydropyran itself gave a hydrazone. The elimination of amides to form olefinic compounds has been demonstrated only under more drastic conditions.[13] $\beta$-substituted tetrahydropyrans would not be expected to give the above products under our mild conditions.

The reaction of amides with dihydropyran quite likely occurred with initial protonation of dihydropyran in the beta position followed by attack of the electron pair of nitrogen at the resonance stabilized positive center in the alpha position. This pyranylation reaction affords *N*-(2-tetrahydropyranyl)-amides. These are the cyclic analogs of the intermediates postulated in the reaction of amides with alicyclic vinyl ethers.

The products of the reactions with dihydropyran were in several cases extremely difficult to crystallize presumably due to product contamination by starting materials. Infrared analysis of the crude products indicated higher yields of product than was possible to isolate. The yields given are dependent upon ease of isolation of products and are not necessarily related to the extent of reaction. Difficulties in crystallization and the presence of sirupy oils suggested the polymerization of dihydropyran in acid medium. Infrared analysis of the crude product from 2,3-dihydropyran and *n*-butyramide indicated a high percentage of adduct (68–76%). The only other product detectable by infrared analysis in the crude mixtures was starting amide. This also was the only other material isolated from the reaction mixtures (see preparation of *N*,*N*-dimethylurea adduct).

(7) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, 69, 2246 (1947).

(8) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, 70, 4187 (1948).

(9) M. Pinner, *Ber.*, 16, 356, 1644 (1883).

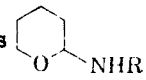
(10) S. M. McElvain and B. Fajardo-Pinzon, *J. Am. Chem. Soc.*, 67, 690 (1945).

(11) R. Zelinski, A. Verbiscar, and H. J. Eichel, *J. Org. Chem.*, 23, 184 (1958).

(12) M. M. Kreevoy, C. R. Morgan, and R. W. Taft, *J. Am. Chem. Soc.*, 82, 3064 (1960).

(13) W. J. Bailey and C. N. Bird, *J. Org. Chem.*, 23, 996 (1958).

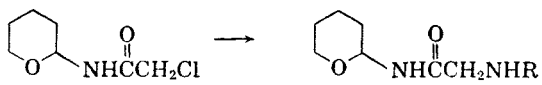
TABLE I

*N*-(2-TETRAHYDROPYRANYL)AMIDES 

| R | Yield, % | M.P. | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N |
| $C_6H_5C(=O)-$ | 73 | 124.0–125.0 | 70.22 | 7.37 | 6.82 | 70.21 | 7.41 | 6.55 |
| $4\text{-}NO_2C_6H_4C(=O)-$ | 53 | 179.0–179.5 | 57.60 | 5.64 | 11.19 | 56.91 | 5.87 | 11.02 |
| $4\text{-}CH_3C_6H_4C(=O)-$ | 21 | 117.0–118.0 | 71.25 | 7.82 | 6.38 | 70.57 | 7.65 | 6.13 |
| $CH_3C(=O)-$ | 37 | 119.5–121.0 | 58.72 | 9.15 | 9.78 | 58.69 | 9.17 | 9.71 |
| $CH_3CH_2CH_2C(=O)-$ | 36 | 51.5–52.5 | 63.13 | 10.01 | 8.17 | 62.64 | 10.26 | 8.01 |
| $(CH_3)_2CHC(=O)-$ | 57 | 111.0 | 63.13 | 10.01 | 8.17 | 62.90 | 10.03 | 7.91 |
| $ClCH_2C(=O)-$ | 63 | 94.0–95.0 | 47.57 | 6.81 | 7.89 | 47.50 | 6.73 | 8.20 |
| $(CH_3)_2NC(=O)-$ | 37 | 121.5–122.5 | 55.78 | 9.36 | 16.27 | 55.82 | 9.47 | 16.10 |
| $4\text{-}CH_3C_6H_4SO_2$ | 22 | 106.0–107.5 | 56.44 | 6.71 | 5.49 | 56.60 | 6.60 | 5.69 |

It is interesting to note the variety of amides that do undergo this reaction. These include (1) aromatic amides with electron donating and withdrawing substituents, (2) alkyl amides—simple, branched, and substituted by electronegative groups, (3) ureas, (4) sulfonamides, and (5) imides (saccharin).

This reaction is of interest as it provides a convenient synthesis of deoxypyranoside and -furanoside analogs of intermediates in purine nucleoside biosynthesis.[14] Replacement of the chlorine in *N*-(2-tetrahydropyranyl)-2-chloroacetamide by various substituted amines gives these biologically important compounds. For example, *N*-(2-tetrahydropyranyl)-2-amino- and *N*-(2-tetrahydropyranyl)-2-allylaminoacetamide were prepared from the corresponding chloro compound by the Gabriel synthesis and direct substitution by allylamine, respectively.



R = H, $CH_2{=}CH{-}CH_2{-}$

## EXPERIMENTAL[15]

*N-(2-Tetrahydropyranyl)amides.* The method used for *N*-(2-tetrahydropyranyl)acetamide is representative. One-half milliliter of ethyl ether saturated with hydrogen chloride was added to a stirred mixture of acetamide (11.8 g., 0.2 mole) and 2,3-dihydropyran (16.8 g., 0.2 mole) in benzene (50 ml.) at room temperature. The mixture was then refluxed for 2 hr. and the clear yellow solution allowed to cool to room temperature. The mixture was neutralized with solid anhydrous sodium carbonate and the solid removed by filtration. Recrystallization of the product, after removal of the solvent, from ether-benzene gave *N*(-2-tetrahydropyranyl)-acetamide (10.5 g., 37%) m.p. 119.5–121.0°. Useful solvents used for recrystallizations include ether, benzene, ether-benzene, benzene-hexane, and benzene-methanol. In many cases, long periods of standing are necessary for crystallization to occur. Reactions with *n*-butyramide, isobutyramide, benzamide, and *p*-toluenesulfonamide were run using the above procedure.

The following method is representative of those instances where use of dimethylformamide solvent or chromatography was necessary. A solution of *N*,*N*-dimethylurea (8.8 g., 0.1 mole), 2,3-dihydropyran (8.4 g., 0.1 mole), and 0.5 ml. of ethyl ether saturated with hydrogen chloride in dimethylformamide (100 ml.) was heated to 90–95° for 2 hr. The solvent was removed and the residue heated with benzene (100 ml.). The mixture was filtered to give 4.1 g. of yellow solid which was shown to be *N*,*N*-dimethylurea by infrared analysis. The filtrate was chromatographed on a 5 × 10 cm. Fisher A540 alumina column with 30:220 ethanol-benzene to give *N'*-(2-tetrahydropyranyl)-*N*,*N*-dimethylurea (6.4 g., 37%). One recrystallization from benzene gave a m.p. of 121.5–122.5°. Complete solution should be insured by addition of sufficient amounts of dimethylformamide when benzene is used as the reaction solvent. Reactions with α-chloroacetamide, *p*-nitrobenzamide, and *p*-toluamide used the above described procedure.

*Base hydrolysis of N-(2-tetrahydropyranyl)benzamide.* *N*-(2-Tetrahydropyranyl)benzamide (10.25 g., 05 mole) was dissolved in 1:1 ethanol-methanol (200 ml.) and sodium hydroxide (2.0 g.) in water (10 ml.) added. The solution was refluxed for 5.5 hr., let stand for 2 days, and then refluxed for an additional 4 hr. The solvent was removed under vacuum and water (100 ml.) added. The water layer was extracted with ether (750 ml.). The water layer showed no positive test for aldehyde with 2,4-dinitrophenylhydrazine. The ether

(14) S. C. Hartman, B. Levenberg, and J. M. Buchanan, *J. Am. Chem. Soc.*, 77, 501 (1955).

(15) All melting points are uncorrected.

layer was evaporated to 125 ml. and washed with 100 ml. of 5% sodium hydroxide. After drying over magnesium sulfate the solution was evaporated to give a colorless solid 7.0 g., m.p. 114–116°. The infrared spectrum was identical with that of the starting adduct.

*Acid hydrolysis of N-(2-tetrahydropyranyl)benzamide.* *N*-(2-Tetrahydropyranyl)benzamide (5.1 g., 0.025 mole) was dissolved in a minimum amount of hot ethanol and added to 2,4-dinitrophenylhydrazine reagent prepared with phosphoric acid (100 ml.).[16] The solution was heated on the steam bath for 15 min. and let stand for one day. After adding water (150 ml.) and ethanol (50 ml.), the yellow orange precipitate was filtered, washed with 1:1 ethanol-water and dried to give 6.1 g. (87%) m.p. 107–108°. Recrystallization of the dried precipitate from ethanol gave the 2,4-dinitrophenylhydrazone derivative of 5-hydroxyvaleraldehyde, m.p. 112–113°. This was identical with an authentic sample. The filtrate was extracted with 600 ml. of ether. The ether extract was extracted with 600 ml. of 5% sodium hydroxide. After drying, the ether extract was concentrated to give 1.5 g. of reddish crystals which upon recrystallization from ether gave colorless crystals of benzamide, m.p. 128–129°. Acidification of the base extract gave no precipitate. The base layer was extracted with ether (500 ml.). After drying, the ether layer was concentrated to give 0.4 g. of additional benzamide (total yield 1.9 g., 63%). Treatment of the benzamide-dihydropyran adduct in ether with hydrogen chloride gave no hydrochloride salt. The adduct was recovered unchanged.

*Saccharin adduct.* The usual method was used to treat saccharin (18.3 g., 0.1 mole) and dihydropyran (17.0 g., 0.2 mole), in benzene (75 ml.). After refluxing the mixture for 17 hr. the reaction mixture deposited white crystals, 22.4 g. (84%) m.p. 137.0–138.5°.

*Anal.* Calcd. for $C_{12}H_{13}NO_4S$: N, 5.24; S, 12.00. Found: N, 5.70; S, 11.46.

*N-(2-Tetrahydropyranyl)-2-phthalimidoacetamide.* *N*-(2-Tetrahydropyranyl)-2-chloroacetamide (17.8 g., 0.1 mole) in dimethylformamide (50 ml.) was added with stirring to a heated (50°) slurry of potassium phthalimide (18.5 g., 0.1 mole) in dimethylformamide (75 ml.). The mixture was heated at 65–70° for 2 hr. and poured into water (250 ml.). The solid was removed by filtration, washed with water (500 ml.) and dried to give crude *N*-(2-tetrahydropyranyl)-2-phthalimidoacetamide (25.9 g., 90%) m.p. 221.4–222.4°. Two recrystallizations of the crude material from absolute ethanol gave a m.p. of 231.4–232.0°.

*Anal.* Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59. Found: C, 62.41; H, 5.53.

*N-(2-Tetrahyaropyranyl)-2-aminoacetamide hydrochloride.* A mixture of *N*-(2-tetrahydropyranyl)-2-phthalimidoacetamide (14.4 g., 0.05 mole) and 85% hydrazine hydrate solution (3.0 g.) was refluxed for 2 hr. Hydrochloric acid (38%, 5.0 g.,0.05 mole) was added after cooling to 40° and the mixture stirred for 10 min. The mixture was cooled to 25° and filtered. The filtrate was evaporated under an air stream and the remaining residue extracted with absolute ethanol (5 × 200 ml.). Successive removal of the solvent from the extract gave *N*-(2-tetrahydropyranyl)-2-aminoacetamide hydrochloride (8.0 g., 82%) m.p. 167–172°. Two recrystallizations of the salt from ethanol gave m.p. 168.8–169.2°.

*Anal.* Calcd. for $C_7H_{15}ClNO_2$: C, 43.19; H, 7.77; Cl, 18.21. Found: C, 43.22; H, 7.34; Cl, 18.01.

*N-(2-Tetrahydroypranyl)-2-aminoacetamide.* *N*-(2-Tetrahydropyranyl)-2-aminoacetamide hydrochloride (1.0 g.) and Amberlite resin IRA 400 (10.0 g.) were stirred together at room temperature in water (50 ml.) for 45 min. The mixture was filtered and the resin washed with water. The aqueous solution was concentrated to give crude *N*-(2-tetrahydropyranyl)-2-aminoacetamide as an amber oil (0.7 g.). The above compound was treated with picric acid in ethanol to form the yellow picrate salt, after two recrystallizations from ethanol, m.p. 159.8–161.8°.

*Anal.* Calcd. for $C_{13}H_{17}N_5O_9$: C, 40.31; H, 4.42; N, 18.09. Found: C, 40.25; H, 4.72; N, 18.21.

*N-(2-Tetrahydropyranyl)-2-allylaminoacetamide.* *N*-(2-Tetrahydropyranyl)-2-chloroacetamide (35.5 g., 0.2 mole) was added in small portions to a solution of allylamine (22.8 g., 0.4 mole) in ether (100 ml.) over 15 min. while cooling to 5°. Stirring was maintained for 3.5 hr. at 5°, the ice bath lowered, and the mixture allowed to stand overnight. The ether layer was decanted and the residue extracted with ether (5 × 100 ml.). Removal of the ether from the combined ether extracts gave crude *N*-(2-tetrahydropyranyl)-2-allylaminoacetamide as an amber oil (16.0 g.).

The above compound was treated with picric acid in ethanol to form a yellow picrate. Two recrystallizations of the picrate from ethanol gave the pure salt, m.p. 154.6–155.0°.

*Anal.* Calcd. for $C_{16}H_{21}N_5O_9$: C, 44.96; H, 4.95; N, 16.39. Found: C, 44.82; H, 5.31; N, 16.78.

*Acknowledgment.* We are indebted to Dr. B. Katlafsky and Mr. O. Kinast for infrared spectra, and to Messrs. J. L. O'Sullivan and O. S. Kring for the analytical data.

St. Louis, Mo.

(16) This reagent was prepared by dissolving 5.0 g. of 2,4-dinitrophenylhydrazine in 60 ml. of 85% phosphoric acid and 40 ml. of 95% ethanol.