[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

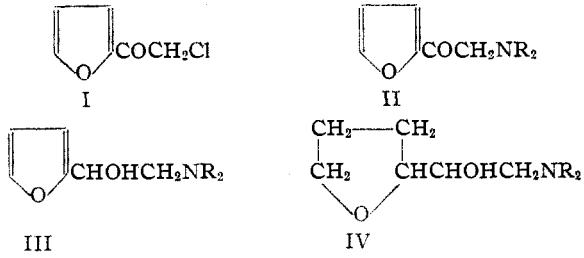
Tetrahydrofuryl Amino Alcohols

BY ALFRED BURGER AND GRANT H. HARNEST[1]

In order to test the significance of the cyclic ether system in morphine for the analgesic activity of the alkaloid, we recently prepared several tertiary tetrahydropyranyl amino alcohols one of which exhibited marked analgesia in animals.[2] We are now reporting the synthesis of a few tetrahydrofuran derivatives containing analogous side chains. These compounds (IV) could be expected to be of interest as potential analgesics since hydrogenolysis of the dihydrofuran ring in morphine causes a decreased activity of the compound with the ether bridge opened.[3]

As a starting material for the synthesis of 2-furyl-α-amino alcohols, 2-chloroacetylfuran (I) was needed. This compound had been prepared by chloroacetylation of furan.[4] We found it more convenient to convert commercial 2-furoic acid to the chloro ketone through the chloride and diazo ketone.

Exchange of the halogen atom in I with tertiary amino groups proceeded smoothly, but the reduction of the α-amino ketones (II) with hydrogen activated by nickel or platinum did not lead to homogeneous compounds; more than three moles of hydrogen was absorbed in most cases. Therefore, aluminum isopropoxide was chosen as a reducing agent. Only the keto group was reduced, nuclear hydrogenation was avoided and reductive elimination of the amino group was also largely suppressed. The best results were obtained when the amino ketone hydrochlorides and not the free bases were used, perhaps because the salts go into solution only gradually in the reagent.



The 2-furyl-α-aminoalcohols (III) were hydrogenated in the presence of Raney nickel under ordinary pressure. The resulting tetrahydrofuryl amino alcohols (IV) are being tested by Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School.

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(1) Smith, Kline and French Research Fellow, 1941–1943

(2) Harnest and Burger, THIS JOURNAL, **65**, 370 (1943).

(3) Ref. 2, footnote 2, p. 26.

(4) Gilman and Burtner, THIS JOURNAL, **57**, 909 (1935).

Experimental

2-Chloroacetylfuran.—A solution of 101 g. of furoyl chloride[5] in 100 cc. of absolute ether was dropped into an ice-cold ether solution of 65 g. of diazomethane; vigorous evolution of nitrogen occurred. After all the acid chloride had been added, the solution was allowed to warm to room temperature and to stand overnight. Most of the ether was removed by distillation and finally by an air jet, leaving a bright yellow oil which crystallized at low temperature. It melted below room temperature, and the crude diazo ketone was therefore converted to the chloro ketone without further purification.

The concentrated ether solution of 2-diazoacetylfuran was cooled in an ice-bath, stirred vigorously, and treated with concentrated hydrochloric acid until acid to congo red. A cold concentrated solution of potassium carbonate was added to neutralize the excess acid, the oily chloro ketone extracted into ether and dried over sodium sulfate. After evaporation of the solvent the chloro ketone was distilled rapidly. The yield of the fraction boiling at 93–108° (4 mm.) was 99.1 g. (88% based on furoyl chloride, 65.5% based on crude 2-furoic acid). Pure 2-chloroacetylfuran crystallizes below 0°.

Preparation of Tertiary 2-(1-Oxo-2-aminoethyl)-furans (II).—An ice-cold solution of one-half mole of the secondary amine in 100 cc. of ether was treated slowly with a solution of 0.2 mole of 2-chloroacetylfuran in 100 cc. of ether. The amine hydrochloride separated rapidly, and the mixture was kept at 0° for one hour, allowed to warm to room temperature and to stand overnight. It was washed with water, the ether solution dried over sodium sulfate, the solvent distilled on the water-bath, and any unreacted secondary amine removed by heating at 18 mm. and 100°. The amino ketones studied were sparingly soluble in water, except 2-(1-oxo-2-morpholinoethyl)-furan. They were usually purified by distillation under 4 mm. pressure, and for further purification converted to the hydrochlorides with dry hydrogen chloride in acetone-ether solution.

Reduction of the Amino Ketones.—In a 200-cc. round-bottom flask equipped with a 1-m. fractionating column filled with glass helices was placed 10–12 g. of the amino ketone hydrochloride[6] and a 200% excess of a 3 *N* aluminum isopropoxide solution, and C. P. isopropyl alcohol was added to make a total volume of about 140 cc. After the mixture had refluxed gently for sixty to ninety minutes and much of the amino ketone hydrochloride had dissolved, the rate of boiling was increased to permit the acetone to distil. When the 2,4-dinitrophenylhydrazine test for acetone became negative, gentle refluxing was resumed for another ninety minutes. Some acetone distilled again. The reduction was complete at this point as shown by the fact that no more acetone was produced when the mixture was boiled for another hour. Most of the isopropyl alcohol was removed under 100-mm. pressure, the viscous residue digested with an excess of 10 *N* sodium hydroxide solution with heating and stirring until all the aluminum salts had gone into solution, the mixture was extracted with ether, and the extract dried over sodium sulfate. The ether was distilled on a steam-bath, and the amino alcohol (III) purified by distillation. The hydrochlorides were prepared in acetone solution.

Nuclear Hydrogenation.—The alkamine hydrochlorides absorbed usually 2.3–2.4 moles of hydrogen in ethanol solution in the presence of Raney nickel in the course of

(5) Hartman and Dickey, *Ind. Eng. Chem.*, **24**, 151 (1932).

(6) The reaction was also carried out with as little as 2 g. in the same apparatus.

TABLE I

PROPERTIES OF FURAN DERIVATIVES, R = FURAN

R	B. p., °C.	Mm.	Yield, %[a]	Hydrochloride M. p., °C.	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-(1-Oxo-2-piperidinoethyl)	139–140	4	73	264–266[b]	$C_{11}H_{16}ClNO_2$	57.51	57.43	7.02	7.32
2-(1-Hydroxy-2-piperidinoethyl)	127–128	5	38	172–174	$C_{11}H_{18}ClNO_2$	57.01	56.73	7.83	8.15
2-(1-Hydroxy-2-piperidinoethyl)-tetrahydro	125–126	4	64	170–173[c]	$C_{11}H_{22}ClNO_2$	56.04	55.79	9.41	9.69
2-(1-Acetoxy-2-piperidinoethyl)-tetrahydro	.....	..	..	191–194	$C_{13}H_{24}ClNO_3$	...	...	5.04[d]	5.37[d]
2-(1-Oxo-2-morpholinoethyl)	.....	..	49	221–229[b]	$C_{10}H_{14}ClNO_3$	51.84	51.86	6.09	6.58
2-(1-Hydroxy-2-morpholinoethyl)	146–150	5[e]	70[f]	185–186[b]	$C_{10}H_{16}ClNO_3$	51.39	51.59	6.90	7.20[g]
2-(1-Acetoxy-2-morpholinoethyl)	.....	..	..	166–167[b]	$C_{12}H_{18}ClNO_4$	52.27	52.48	6.58	6.62
2-(1-Hydroxy-2-morpholinoethyl)-tetrahydro[h]	138–140	12	41	170–176	$C_{10}H_{20}ClNO_3$	50.52	51.57	8.48	7.86
2-[1-Oxo-2-(4-methylpiperidino)-ethyl]	133–139	4	51	253–265	$C_{12}H_{18}ClNO_2$	59.13	59.01	7.44	7.69
2-[1-Hydroxy-2-(4-methylpiperidino)-ethyl]	126–128	4	74[f]	70–72[f]	$C_{12}H_{19}NO_2$[f]	68.86	68.76[f]	9.15	9.45[f]
2-[1-Acetoxy-2-(4-methylpiperidino)-ethyl]	.....	..	..	179–181[b]	$C_{14}H_{22}ClNO_3$	...	...	4.86[d]	4.96[d]
2-[1-Hydroxy-2-(4-methylpiperidino)-ethyl]-tetrahydro	131–132	4	33[f]	.....	$C_{12}H_{23}NO_2$[f]	...	...	6.57[d]	6.78[d,f]
3-(1-Keto-3-dimethylaminopropyl)-2,5-dimethyl[i]	.....	..	..	175–177	$C_{11}H_{18}ClNO_2$	...	...	6.04[d]	5.97[d]

[a] Yields of hydrochloride are reported, whenever oily bases were converted to hydrochloride for purification. [b] With decomposition. [c] Mixed melting point with hydrochloride just above showed a 20° depression. [d] Nitrogen analysis. [e] M. p., 67–68°; purified by sublimation at 70° (1 mm.). [f] Free base. [g] Nitrogen analysis on free base: calcd., 7.10; found, 7.09. [h] Hydrochloride hygroscopic. [i] Prepared by the Mannich reaction from 2,5-dimethyl-3-acetylfuran, paraformaldehyde and dimethylamine hydrochloride. Recrystallized from ethanol–ether.

ten to twelve hours. The catalyst was filtered off, the solvent evaporated under reduced pressure, the bases were liberated with alkali and extracted into ether. The tetrahydrofuryl amino alcohols (IV) were purified by fractional distillation. They appeared as colorless oils and were submitted for pharmacological tests except in those cases in which crystalline salts could be prepared.

Acetyl Derivatives.—Acetylation of the furyl and tetrahydrofuryl amino alcohols was carried out by heating the free bases with an excess of acetic anhydride at 100° for one hour. The hydrochlorides usually crystallized when ethereal hydrogen chloride was added to the reaction mixture.

Summary

Tetrahydrofuran derivatives containing tertiary α-amino alcohol groups in position-2 were prepared in a systematic study of potential analgesics.

2-(1-Oxo-2-dialkylaminoethyl)-furans were reduced to the corresponding amino alcohols with aluminum isopropoxide, and nuclear hydrogenation was accomplished by use of Raney nickel catalyst at ordinary pressure.

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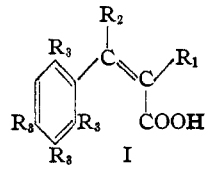
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Olefins. VIII. The Synthesis and Resolution of Certain β-Substituted-β-arylacrylic Acids

BY ROGER ADAMS AND C. W. THEOBALD[1]

A comparison of the effect of varying the R_2 group upon the rate of racemization of hindered acrylic acid molecules of Type I has not been made previously. This has now been under-



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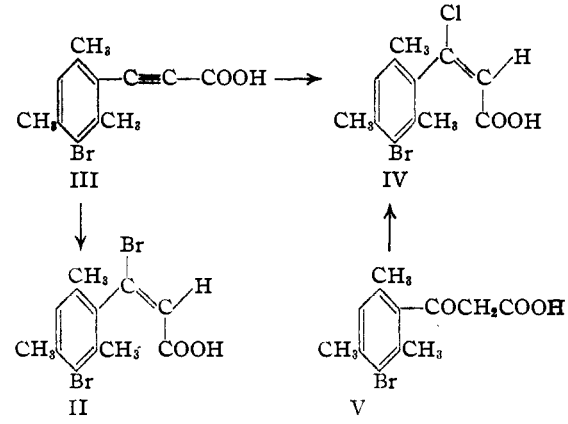
taken, since a feasible method of synthesis for such molecules has been devised.[2]

β-Bromo-β-(3-bromo-2,4,6-trimethylphenyl)-acrylic acid (II), made by addition of hydrogen bromide to 3-bromo-2,4,6-trimethylphenylpropiolic acid (III), was resolved and the rate of racemization determined and compared with that of β-chloro-β-(3-bromo-2,4,6-trimethylphenyl)-acrylic acid (IV)[3] synthesized by the action of phosphorus pentachloride on 3-bromo-2,4,6-trimethylbenzoylacetic acid (V) or by the addition



III IV

II V

(1) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry: Eastman Kodak Fellow, 1942–43.

(2) Adams and Theobald, THIS JOURNAL, **65**, 2208 (1943).

(3) Adams, Anderson and Miller, *ibid.*, **63**, 1589 (1941).