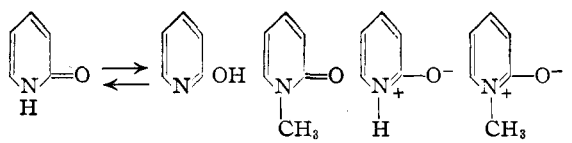
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Triarylpyridylmethanes

BY ROGER ADAMS, JACK HINE AND JOHN CAMPBELL

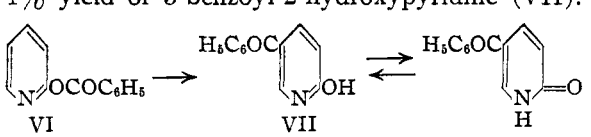
The absorption spectra of 2-pyridone (I) or its tautomer, 2-hydroxypyridine (II) and 1-methyl-2-pyridone (III) are very similar and suggest an analogous formulation. A considerable contribution of a "Zwitterion" resonance form of each (IV and V) to the total structure of the molecules is compatible with the physical properties of the compounds.[1]



I II III IV V

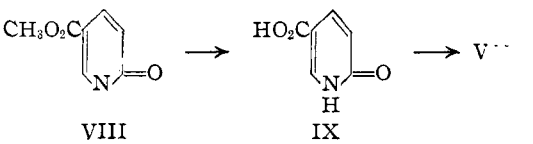
If this proposal is correct, analogous chemical reactivity of IV and V might be anticipated. Such similarity is exemplified in the halogenation,[2,3] nitration,[3,4] sulfonation[5] and arsonation[6] of 1-methyl-2-pyridone which leads to 5-mono- or 3,5-disubstituted products analogous to those obtained from 2-pyridone or 2-hydroxypyridine with the same reagents. Attempts to apply the Friedel and Crafts reaction with acyl and aroyl halides failed probably because of the complexing of the catalysts, aluminum chloride or boron trifluoride, with the pyridones. Thiocyanation and nitrosation were also unsuccessful.

The application of the Fries rearrangement to the O-benzoate of 2-hydroxypyridine (VI) under the conditions used of fusion of the benzoate with anhydrous aluminum chloride gave only a 1% yield of 5-benzoyl-2-hydroxypyridine (VII).



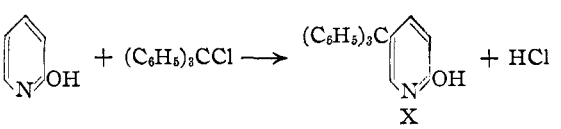
VI VII

The structure of VII was proved by an unequivocal method. Methyl coumalinate (VIII) prepared by esterification of coumalinic acid formed from maleic acid, was converted by ammonia followed with alkali to 2-hydroxypyridine-5-carboxylic acid (IX). This was transformed to VII through the acid chloride and condensation with benzene in the presence of aluminum chloride.



VIII IX

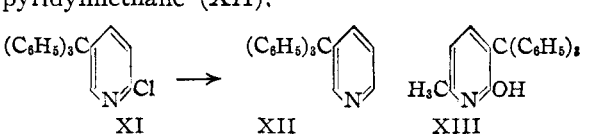
2-Hydroxypyridine or 2-pyridone and 1-methyl-2-pyridone both condensed readily with triphenylchloromethane without catalyst or with triphenylcarbinol in the presence of a little sulfuric acid merely by heating. The N-methyl group in the latter was lost and the same product resulted, 5-triphenylmethyl-2-hydroxypyridine (X). The position of the triphenylmethyl radical is assumed on the basis of that taken by other groups when substituted in 2-hydroxypyridine. Thus, the reaction resembles that which



X

occurs between triphenylchloromethane or triphenylcarbinol and phenols or aromatic amines. The carbonium ions so readily formed from triphenylmethyl derivatives may account for the ease of substitution.

5-Triphenylmethyl-2-hydroxypyridine is transformed almost quantitatively by the action of phosphorus oxychloride in a sealed tube to 5-triphenylmethyl-2-chloropyridine (XI). The latter upon catalytic reduction yields triphenylpyridylmethane (XII).



XI XII XIII

The reaction appears to be a fairly general one. Triphenylchloromethane reacts readily with 3-methyl-2-hydroxypyridine, and diphenylxenylchloromethane or the corresponding carbinol reacts with 2-hydroxypyridine and with its 3-methyl derivative. The yields were 45–60% in all cases. 6-Methyl-2-hydroxypyridine, however, condenses with triphenylchloromethane to give only a 9% yield of product although with the carbinol a 22% yield results. It is assumed that the triphenylmethyl group has probably entered the 3-position (XIII) in this case since the condensation product unlike all the others could not be converted to the chloropyridine and is insoluble in aqueous ethanolic sodium hydroxide, presumably because of the steric hindrance of the *o*-triphenylmethyl group.

5-Triphenylmethyl-2-hydroxypyridine reacts similarly to 2-hydroxypyridine with organic

(1) Specker and Gaurosch, *Ber.*, **75B**, 1338 (1942); see also Baker and Baly, *J. Chem. Soc.*, **91**, 1126 (1906); v. Auwers, *Ber.*, **63B**, 2111 (1936); Arndt and Kalischek, *ibid.*, **63B**, 587 (1930); Arndt, *ibid.*, **63B**, 2963 (1930); Hückel, *Z. Elektrochem.*, **43**, 752 (1937).

(2) Dohrn and Thiele, German Patent 500,915; *Frdl.*, **17**, 2440 (1932).

(3) Fischer and Chur, *J. prakt. Chem.*, [2] **93**, 363 (1916).

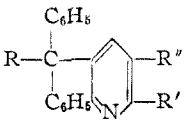
(4) Chichibabin and Konowalowa, *Ber.*, **58**, 1712 (1925).

(5) (a) v. Schickh, German Patent 601,896; *Frdl.*, **21**, 517 (1937); (b) Naegeli, Kündig and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938); Haack, German Patent 597,452; *Frdl.*, **21**, 518 (1937).

(6) Binz, Räth and Maier-Bode, *Ann.*, **478**, 22 (1930).

TABLE I

TRIARYLPYRIDYLMETHANES



R	R′	R″	Yield, %	Solvent[a] for rexl.	M. p.,[b] °C. (cor.)	Formula	Percentage composition Calcd. C	H	N	Cl	Found C	H	N	Cl
C_6H_5–	–OH	–H	48	A	365–368	$C_{24}H_{19}ON$	85.43	5.68	4.15		85.18	6.02	4.15	
C_6H_5–	–OH	$–CH_3$	54	E	260–262	$C_{25}H_{21}ON$	85.43	6.02	4.00		85.23	6.22	4.18	
p-$C_6H_5C_6H_4$–	–OH	–H	58	B	298–300	$C_{30}H_{23}ON$	87.13	5.61	3.39		87.04	5.86	3.21	
p-$C_6H_5C_6H_4$–	–OH	$–CH_3$	56	B, E	307–310	$C_{31}H_{25}ON$	87.08	5.89	3.28		87.14	6.13	3.46	
C_6H_5–	–Cl	–H	88	B, E	256–257	$C_{24}H_{18}NCl$	81.00	5.10	3.94	9.96	81.03	4.92	3.84	9.78
C_6H_5–	–Cl	$–CH_3$	92	L	130[c]	$C_{25}H_{20}NCl$	81.18	5.45	3.79		81.41	5.20	4.01	
p-$C_6H_5C_6H_4$–	–Cl	–H	95	B, L	182–183	$C_{30}H_{22}NCl$	83.41	5.13	3.24	8.21	83.59	5.42	3.23	8.05
p-$C_6H_5C_6H_4$–	–Cl	$–CH_3$	93	E	158–159	$C_{31}H_{24}NCl$	83.48	5.42	3.14	7.95	83.20	5.62	2.90	8.00
C_6H_5–	–H	–H	66	B, E	269–270	$C_{24}H_{19}N$	89.68	5.96	4.36		89.45	6.30	4.51	
C_6H_5–	–H	$–CH_3$	83	E	153–154	$C_{25}H_{21}N$	89.51	6.31	4.18		89.54	6.24	4.40	
p-$C_6H_5C_6H_4$–	–H	–H	91	E	195–196	$C_{30}H_{23}N$	90.64	5.83	3.53		90.22	5.93	3.40	
p-$C_6H_5C_6H_4$–	–H	$–CH_3$	91	E	188–189	$C_{31}H_{25}N$	90.48	6.12	3.40		90.23	6.23	3.55	

[a] Solvents as follows: A = glacial acetic acid, B = benzene, E = absolute ethanol, L = ligroin (b. p. 80–110°). Combinations denote recrystallization from mixed solvents. [b] All melting points above 200° were taken in a melting point block. [c] Double m. p.—solidified and remelted at 151–152°.

halides in alkaline solution. It is converted with potassium hydroxide and chloroacetic acid into N-carboxymethyl-5-triphenylmethyl-2-pyridone.

Triphenylpyridylmethane, like tetraphenylmethane, has a high melting point of 269–270°. Its solubility characteristics are likewise almost identical, insoluble in ether and petroleum ether, very slightly soluble in hot ethanol and glacial acetic acid and soluble in hot benzene.

It exhibits a marked phosphorescence after irradiation with ultraviolet light at room temperature. The brilliant blue-green afterglow from tetraphenylmethane has a visible duration of twenty-three seconds[7] and the greenish-white afterglow from triphenylpyridylmethane only one second.

The infrared absorption spectra of triphenylpyridylmethane and tetraphenylmethane are similar as shown in Chart I. In the infrared absorption spectra the CH deformational frequencies (1450, 1470 cm.$^{-1}$) and phenyl frequencies (1490, 1598 cm.$^{-1}$) are almost identical. Curve II shows additional absorption characteristics of the pyridine at 1412, 1570 and 1588 cm.$^{-1}$.

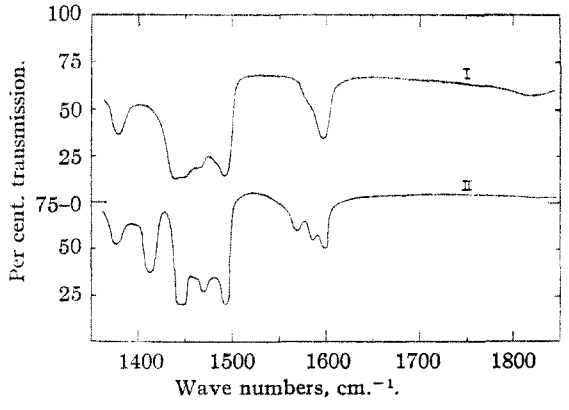


Fig. 1.—Curve I, tetraphenylmethane; Curve II, triphenyl-β-pyridylmethane. Both compounds were examined in mineral oil paste.

(7) Clapp, THIS JOURNAL, **61**, 523 (1939).

The properties of the various pyridones and pyridines are recorded in Table I.

Experimental

2-Pyridyl-*p*-nitrobenzenesulfonate.—To 7.3 g. of melted *p*-nitrobenzenesulfonyl chloride was added slowly 3.86 g. of anhydrous sodium 2-hydroxypyridine. An exothermic reaction occurred. When this had subsided, the vessel was heated and the contents stirred, dissolved in benzene, filtered, and petroleum ether added to the cloud point. The solution was cooled, and the light yellow crystals which were removed by filtration weighed 7.4 g. (80%). Decolorization with Norit and two recrystallizations from benzene yielded material of m. p. 157–160° (cor.).

Anal. Calcd. for $C_{11}H_8O_5N_2S$: C, 47.17; H, 2.87; N, 10.00. Found: C, 47.33; H, 2.92; N, 9.83.

2-Pyridyl Benzoate from Sodium 2-Hydroxypyridine and Benzoyl Chloride.—This compound was prepared by a method somewhat different from any of the three used by Chichibabin and Oparina.[8] To 11.7 g. of anhydrous sodium 2-hydroxypyridine was added 15.0 g. of freshly redistilled benzoyl chloride. Heat was evolved, and a reddish color developed. The material was heated to 200° for an hour to complete the reaction and then distilled in vacuum. After a slight forerun, most of the remainder of the material was collected at 180–190° (25 mm.). The colorless liquid crystallized to a white solid which weighed 17 g. (85%) and melted at 35–40°.

2-Pyridyl Benzoate from Benzoyl Chloride and 2-Hydroxypyridine in Pyridine.—A solution of 14.1 g. of freshly redistilled benzoyl chloride and 4.75 g. of 2-hydroxypyridine in 39.5 (0.5 mole) of pyridine was refluxed for three hours. The solution was then distilled until the overhead temperature reached 120° in order to remove most of the pyridine. The residue was poured on ice and the mixture extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and distilled under vacuum. The material distilling between 180–195° (30

(8) Chichibabin and Oparina, *J. Russ. Phys.-Chem. Soc.*, **56**, 153 (1925).

mm. pressure) was collected and found to weigh 9.0 g. (90%). The yellow liquid began to crystallize when cooled to 30°, and was completely solid at 15°. It was identified as 2-pyridyl benzoate by its boiling point and by hydrolysis to benzoic acid. No crystals were obtained from the small amount of residue from the vacuum distillation.

Fries Reaction with 2-Pyridyl Benzoate.—To 11.1 g. of 2-pyridyl benzoate (m. p. 35–40°) was added 27 g. of freshly resublimed aluminum chloride. The material was stirred and heated by an oil-bath which was maintained at 180° for three hours. After the reaction mixture had cooled it was poured on ice. At this point the odor of benzoyl chloride was quite evident. The aqueous suspension was boiled and filtered. The precipitate was extracted with ether and filtered. The ether solution in turn was extracted with sodium bicarbonate in order to remove benzoic acid. The ether was evaporated, and the residue dried in a vacuum desiccator. It was then recrystallized from a mixture of chloroform and ligroin, yielding 0.09 g. (0.81%) of brown crystals melting at 152–170° (cor.). These were sublimed in vacuum at about 160° to give cream colored crystals, which were recrystallized from aqueous ethanol to give almost white crystals sintering at 188° and melting at 194–196° (cor.). The melting point of a mixture of this material with the 5-benzoyl-2-hydroxypyridine prepared from 2-hydroxypyridine-5-carboxylic acid showed no depression. The infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.54; N, 7.07.

5-Benzoyl-2-hydroxypyridine.—This was prepared from 2-hydroxypyridine-5-carboxylic acid in a manner analogous to the synthesis by Kirpal[9] of 3-benzoyl-2-hydroxypyridine from 2-hydroxypyridine-3-carboxylic acid. To 1.05 g. of 2-hydroxypyridine-5-carboxylic acid[10] was added 3.5 g. of thionyl chloride. The mixture was maintained at a temperature of 80° for forty minutes; then the excess thionyl chloride was removed under vacuum. The acid chloride, after cooling, solidified. It was covered with 17.4 g. of benzene, and 8.0 g. of white, freshly resublimed aluminum chloride was added in several portions with stirring. The solution was refluxed for two hours, cooled, and poured on ice. The resulting solution was steam-distilled to remove the benzene, concentrated and filtered. The precipitate was decolorized with Norit and recrystallized from aqueous ethanol to give 1.0 g. (66%) of yellow crystals. These were sublimed in vacuum at 160°, and recrystallized from aqueous ethanol to give white crystals, m.p. 194–196° (cor.).

2-Chloropyridine-5-sulfonyl Chloride.—To a flask containing 13.5 g. of carefully dried 1-methyl-2-pyridone-5-sulfonic acid[5a] was added 26 g. of phosphorus pentachloride. The flask was heated in an oil-bath. When the temperature reached 110° liquid started to form, and gas was evolved so rapidly that a little material was lost. The oil-bath was kept at a temperature of 125° for two hours, at which time the evolution of gas had almost ceased. The mixture was then cooled to 0°, ground with ice, filtered, dried and found to weigh 11.35 g. (76%). Two recrystallizations from mixtures of petroleum ether (b.p. 50–80°) and benzene yielded white crystals of m.p. 50–51° (cor.). Naegeli, Kündig and Brandenburger[5b] report a melting point of 51.5°.

Anal. Calcd. for $C_5H_3O_3Cl_2NS$: C, 28.30; H, 1.51; N, 6.60. Found: C, 28.35; H, 1.48; N, 6.70.

2-Chloropyridine-5-sulfonamide.—To 11.35 g. of 2-chloropyridine-5-sulfonyl chloride was added 200 ml. of concentrated aqueous ammonia. The mixture was then heated to boiling while 200 ml. of additional concentrated aqueous ammonia was added. The solution was concentrated to 200 ml. and allowed to cool. The white crystals were removed by filtration, dried and found to weigh 6.79 g. (66%). Recrystallization from aqueous ethanol yielded crystals of m.p. 157–159° (cor.). This is the same melting point reported by Naegeli, Kündig and Brandenburger.[5b]

2-Chloropyridine-5-(N-2-pyridyl-sulfonamide).—To 0.140 g. of 2-chloropyridine-5-sulfonyl chloride dissolved in 5 ml. of benzene was added a solution of 0.23 g. of 2-aminopyridine in 5 ml. of benzene. The solution was evaporated and petroleum ether added until most of the benzene had been removed. It was then cooled in the ice-box, collected by filtration, dried, and washed with water to remove aminopyridine and its salts. The product weighed 0.12 g. (66%). Two recrystallizations from ethanol yielded material of m.p. 237–239° (cor.). Chichibabin and Vialatout[11] did not report a melting point.

2-Methoxypyridine-5-sulfonamide.—To a solution of 3 g. of sodium in 50 ml. of methanol, 6.76 g. of 2-chloropyridine-5-sulfonamide was added. The solution was refluxed for about sixty hours, most of the methanol was evaporated, water was added, the solution again concentrated, cooled overnight and filtered. The dark brown odoriferous material obtained was decolorized with Norit and recrystallized from water to yield 5.06 g. (77%). Further decolorization and recrystallization from water yielded white crystals, m.p. 149–150° (cor.).

Anal. Calcd. for $C_6H_9O_3N_2S$: C, 38.29; H, 4.28; N, 14.89. Found: C, 38.54; H, 4.27; N, 14.79.

5-Triarylmethyl-2-hydroxypyridines.—The reaction was carried out in the same fashion in all cases, by heating the 2-hydroxypyridines with the triarylchloromethane or with the triarylcarbinol and a few drops of concentrated sulfuric acid. A typical condensation is the preparation of 5-triphenylmethyl-2-hydroxypyridine.

A mixture of 3 g. of triphenylcarbinol and 3 g. of 2-hydroxypyridine was melted, two drops of concentrated sulfuric acid added and an air-cooled reflux condenser attached to the flask. It was heated in a metal-bath at 250° for twenty minutes, cooled, and 60 ml. of boiling absolute ethanol added. The precipitate was removed by filtration, washed with 30 ml. of hot absolute ethanol and dried to give a light cream-colored powder. Two recrystallizations from glacial acetic acid yielded a white powder, m.p. 365–368° (cor.). The compound is extremely insoluble in most organic solvents. The condensation of hydroxypyridines with triarylchloromethanes without addition of sulfuric acid was carried out under identical conditions. The yields were usually a few per cent. less than those from the carbinols. All the products were insoluble in aqueous 10% sodium hydroxide but readily dissolved upon the addition of an equal volume of ethanol.

In preparing 5-triphenylmethyl-3-methyl-2-hydroxypyridine, the product was soluble in hot ethanol and was recrystallized from the resulting solution with the use of Norit.

3-Triphenylmethyl-6-methyl-2-hydroxypyridine.—The condensation of triphenylcarbinol and 6-methyl-2-hydroxypyridine carried out as above afforded a dark brown product. After decolorizing twice with Norit and recrystallizing from benzene, a white powder was obtained in 22% yield. Only a 9% yield was obtained using triphenylchloromethane in the condensation. Three recrystallizations from benzene gave a product melting at 314–317° (cor.). It was insoluble in aqueous ethanolic sodium hydroxide and was recovered almost quantitatively on attempting to treat it with phosphorus oxychloride as described below.

Anal. Calcd. for $C_{25}H_{21}ON$: C, 85.43; H, 6.02; N, 4.00. Found: C, 85.38; H, 5.86; N, 3.97.

5-Triarylmethyl-2-chloropyridines.—The 5-triarylmethyl-2-hydroxypyridine and phosphorus oxychloride react under the following general conditions. A mixture of the hydroxypyridine and a six-fold excess of phosphorus oxychloride was sealed in a tube and placed on the steam-bath for forty-eight hours. After opening the cooled tube the resulting homogeneous solution was poured onto cracked ice and stirred. The mixture was boiled for

(9) Kirpal, *Monatsh.*, **27**, 371 (1906).

(10) v. Pechmann and Welsh, *Ber.*, **17**, 2384 (1884).

(11) Chichibabin and Vialatout, *Bull. soc. chim. France*, [5] **6**, 736 (1939).

several minutes to coagulate the gelatinous precipitate. The latter was removed by filtration, washed with water, dried, and recrystallized from the appropriate solvent. Yields were nearly quantitative. Refluxing with phosphorus oxychloride or heating with phosphorus pentachloride for forty-eight hours in an open vessel gave a product in only one case, and then in poor yield, indicating that a closed system was essential.

5-Triarylpyridylmethanes.—The 5-triarylmethyl-2-chloropyridines were reduced to the corresponding pyridines by the same general method, using Raney nickel catalyst in ethanolic potassium hydroxide solution. The reductions were run in very dilute solution and at 70° to effect solution of the reactants and products. A typical run is described.

One gram of 5-triphenylmethyl-2-chloropyridine and 0.50 g. of potassium hydroxide were dissolved in 200 ml. of hot absolute ethanol. One-half gram of Raney nickel was added and the mixture shaken for six hours at 70° under 45 lb. hydrogen pressure. After removing the catalyst by filtration the solution was evaporated until it became cloudy. Upon cooling, white crystals separated. Two recrystallizations from benzene–ethanol mixture (1:1) gave a product melting at 269–270° (cor.).

N-Carboxymethyl-5-triphenylmethyl-2-pyridone.—A suspension of 0.80 g. of 5-triphenylmethyl-2-hydroxypyridine, 0.67 g. of chloroacetic acid and 0.85 g. of potassium hydroxide in 25 ml. of absolute ethanol was refluxed for six hours. After removal of precipitated potassium chloride by filtration, the resulting solution was diluted with 25 ml. of water and acidified with hydrochloric acid. The bulky white precipitate which formed was removed by filtration, washed well on the filter with water and dried; yield, 0.84 g. (92%). Two recrystallizations from dioxane gave microscopic white crystals, m.p. 264–266° (cor.) with decomposition. The product forms an emulsion with aqueous 10% sodium hydroxide but dissolves upon the addition of an equal volume of ethanol.

Anal. Calcd. for $C_{26}H_{21}O_3N$: C, 78.97; H, 5.35. Found: C, 79.04; H, 5.04.

Summary

1. The Fries rearrangement has been applied to the O-benzoate of 2-hydroxypyridine. A very small yield of 5-benzoyl-2-hydroxypyridine resulted. The structure of this latter product was determined by an unequivocal synthesis; methyl coumalinate was converted by ammonia followed by alkali to 2-hydroxypyridine-5-carboxylic acid which was transformed into the acid chloride and condensed with benzene in the presence of aluminum chloride.

2. Triphenylchloromethane and diphenylxenylchloromethane condense with 2-hydroxypyridine and 3-methyl-2-hydroxypyridine to give the corresponding 5-triarylmethyl-2-hydroxy- or 5-triarylmethyl - 2 - hydroxy - 3 - methylpyridines. Similar condensations occur with the triarylcarbinols and the 2-hydroxypyridines in presence of a few drops of sulfuric acid. With phosphorus oxychloride the triarylmethyl hydroxypyridines are converted to the chloropyridines which upon reduction yield triarylpyridylmethanes. Triphenylpyridylmethane resembles tetraphenylmethane in physical properties and in its phosphorescence after illumination with ultraviolet light.

3. 6-Methyl-2-hydroxypyridine condenses with triphenylchloromethane or the carbinol in low yields to give a product, presumably 3-triphenylmethyl-6-methyl-2-hydroxypyridine since it is alkali-insoluble and does not react with phosphorus oxychloride.

URBANA, ILLINOIS RECEIVED AUGUST 2, 1948

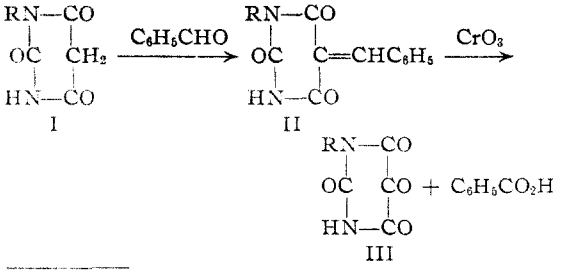
[CONTRIBUTION FROM THE SECTION OF PHARMACOLOGY, THE HEBREW UNIVERSITY AND HADASSAH]

Preparation and Properties of New Derivatives of Alloxan

BY G. BRÜCKMANN[1] AND S. D. ISAACS

The discovery by Shaw-Dunn and co-workers[2] that alloxan causes diabetes in experimental animals by selective destruction of the insulin-producing pancreatic islet cells has evoked considerable interest. An investigation undertaken in this Laboratory of the structural specificity of the effect required the preparation of a number of new members of the series, since the only previously described N-substituted alloxans are the 1-methyl,[3] 1-ethyl,[4] 1-phenyl,[5] 1,3-dimethyl,[6] 1,3-diethyl[7] and 1-methyl-3-ethyl[8] derivatives.

For preparation of several additional derivatives of interest for pharmacological study, an N-substituted urea was first condensed with malonic acid in the presence of acetic anhydride,[9] or with malonic ester in the presence of sodium methoxide (advantageous in the preparation of 1-phenylbarbituric acid). In accordance with the method of Biilman and Berg,[10] the resulting N-substituted barbituric acid (I) was then converted into the benzal derivative (II) and this was oxidized with chromic acid to the alloxan (III) and benzoic



(1) Dr. Brückmann was killed during the War in Israel. The revised version of the paper was prepared by L. F. Fieser.—*The Editor.*

(2) Shaw-Dunn, Sheehan and McLetchie, *Lancet*, **1**, 484 (1943).

(3) Fischer and Clemm, *Ber.*, **30**, 3090 (1897).

(4) Biltz and Sedlatschek, *ibid.*, **57**, 175 (1924).

(5) Winslow, THIS JOURNAL, **61**, 2089 (1939).

(6) Biltz, *Ber.*, **45**, 3659 (1912).

(7) Sembritzki, *ibid.*, **30**, 1821 (1897).

(8) Biltz and Max, *Ann.*, **414**, 95 (1917).

(9) Biltz and Wittek, *Ber.*, **54**, 1035 (1921).

(10) Biilman and Berg, *ibid.*, **63**, 2188 (1930).