(purine ring), 7.30 (methyl hydrogen), 9.25–9.70 (broad C–O–C) μ.

Anal. Calcd. for $C_{19}H_{22}N_4O_9S$: C, 47.30; H, 4.60; S, 6.63. Found: C, 47.57; H, 4.98; S, 6.64.

Amorphous 9-(tetra-*O*-acetyl-β-D-galactofuranosyl)-6-mercaptopurine, 680 mg., was deacetylated in methanolic sodium methoxide made by adding several freshly cut pellets of sodium to the methanolic solution of the blocked nucleoside. The solution was warmed, then evaporated. The residue was redissolved in water, neutralized with glacial acetic acid, diluted with ethanol, and placed on a column (210 × 22 mm.) of Amberlite[22] IRC-50 (H^+). The material was washed from the column with 200 ml. of 50% (v./v.) aqueous ethanol. Evaporation of the eluate left a crystalline mass (VIII) which was treated with carbon in water and the colorless solution was evaporated to a sirup which was dried by codistillation with ethanol. The white crystalline solid obtained was recrystallized from warm ethanol, yielding 200 mg. (45%): m.p. 192–194°; $[\alpha]^{17}D$ −63° (*c* 0.56, water); absorption spectra data[13] $\lambda_{max}^{H_2O}$ 322 mμ; λ_{max}^{KBr} 3.0 (OH), 3.60–3.90 (broad –SH), 6.30, 6.65, 6.90 (purine ring), 9.05–9.75 (broad C–OH) μ; X-ray powder diffraction data[16] 14.85 w, 11.40 w, 9.35 w, 8.76 w, 7.34 m, 6.42 vw, 5.95 w, 5.70 vw, 5.19 s (3), 4.67 s (2), 3.67 s (1), 3.25 s, 2.84 m. Paper chromatography[13] revealed one mobile spot, R_{Ad} 0.52.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S$: C, 42.04; H, 4.49; N, 17.83; S, 10.20. Found: C, 41.47; H, 4.63; N, 17.49; S, 10.70.

9-(β-D-Glucofuranosyl)-6-mercaptopurine (VIIIa).—Ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside[10,23] (4.47 g.) was converted to tetra-*O*-acetyl-β-D-glucofuranosyl chloride[24] (VIa) as described above for the D-galactose analog. The sirupy product was not crystallized but was used immediately in the coupling step with 6-chloro-9-chloromercuripurine as described above for the D-galactose analog except that the toluene mixture was refluxed for 4 hr. The crude product, 6-chloro-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)purine (VIIa), was isolated as a sirup in the same manner with omission of the column chromatography; yield 4.70 g. (85%). Further treatment with decolorizing carbon in methanol gave a glass showing one major spot with a minor trailing spot on thin layer chromatography (silica gel G, water-saturated 1-butanol developer, sulfuric acid indicator): $[\alpha]^{26}D$ −3° (*c* 0.94, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 264 mμ; λ_{max}^{KBr} 6.85 (ester carbonyl), 6.38, 6.50, 6.82 (purine ring), 7.40 (methyl hydrogen), 9.30–9.70 (broad C–O–C) μ.

An amount of 2.0 g. of the above dried, glassy product was converted to the 6-mercapto acetylated derivative with thiourea as described above for the D-galactose analog and the product was isolated in the same manner as an amorphous solid: yield 1.0 g.; m.p. 178–180°; $[\alpha]^{22}D$ −34° (*c* 0.47, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 324 mμ; λ_{max}^{KBr} 3.40 (–SH), 5.80 (ester carbonyl), 6.32, 6.60, 6.85 (purine ring), 7.40 (methyl hydrogen), 9.30–9.70 (broad C–O–C) μ.

The above crude mercapto acetylated derivative (900 mg.) was deacetylated and deionized (by washing with 250 ml. of 50% aqueous ethanol) in the same manner as that described for the corresponding D-galactose derivative. The solid obtained on evaporation of the eluate was dissolved in 95% ethanol (decolorizing carbon) and evaporated to a small volume. Crystallization of VIIIa was effected by allowing the solution to stand at 0°: yield 80 mg.; m.p. 199–199.5°; $[\alpha]^{23}D$ −74° (*c* 0.47, water); absorption spectra data[13] $\lambda_{max}^{H_2O}$ 323 mμ; λ_{max}^{KBr} 3.05 (OH), 3.60–3.80 (SH), 6.32, 6.60, 6.85 (purine ring), 9.52, 9.85 (C–OH) μ; X-ray powder diffraction data[16] 10.10 vw, 8.90 w, 7.14 vw, 5.75 w, 5.39 m, 4.56 w, 4.37 w, 4.08 s (3), 3.53 s (1), 3.41 s (2), 3.16 w. The material showed one spot on paper chromatography,[13] R_{Ad} 0.58.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S$: C, 42.04; H, 4.49; N, 17.83; S, 10.20. Found: C, 42.06; H, 4.49; N, 17.76; S, 10.76.

(22) A product of the Rohm and Haas Co., Philadelphia 5, Pa.

(23) W. Schneider and J. Sepp, *Ber.*, **49**, 2054 (1916); J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, **59**, 1205 (1937); M. L. Wolfrom, S. W. Waisbrot, D. I. Weisblat, and A. Thompson, *ibid.*, **66**, 2063 (1944).

(24) H. H. Schlubach, W. Rauchenberger, and H. Schultze, *Ber.*, **66**, 1248 (1933).

N-Iodohydantoins. II.[1,2] Iodinations with 1,3-Diiodo-5,5-dimethylhydantoin

ORFEO O. ORAZI, RENLE A. CORRAL, AND HÉCTOR E. BERTORELLO[3]

Facultad de Química y Farmacia, Universidad Nacional de La Plata, La Plata, Argentina

Received November 16, 1964

1,3-Diiodo-5,5-dimethylhydantoin, a stable reagent previously described, shows general applicability for nuclear iodination of homo- and heteroaromatic compounds activated by electron-donating substituents. It has been demonstrated, on the basis of isolation of 2-(iodoamino)-4,6-dimethylpyrimidine and 2,4-dimethyl-6-(N-iodo-N-acetylamino)pyrimidine, that the iodination of amino and acetylamino aromatic substrates occurs, at least in some cases, *via* the intermediate formation of N-iodo derivatives. Furthermore, like N-iodosuccinimide, it reacts with enol acetates derived from saturated and unsaturated ketones, affording α-iodo ketones in good yields.

The successful application of a series of N-chloro and N-bromo derivatives of the hydantoin ring as halogenating and oxidizing agents[4] led us to prepare the analogous iodo compounds. 1,3-Diiodo-5,5-dimethylhydantoin (DIH) was the most promising reagent owing to the high iodine content, the very satisfactory stability, and its economical preparation.[1] It is obtained in 74% yield by the reaction of an alkaline aqueous solution of 5,5-dimethylhydantoin with iodine monochloride, thus obviating the expensive silver derivatives commonly used as intermediates in the preparation of N-iodoamides or -imides.

It was previously shown that DIH reacts with 2-ethoxynaphthalene giving a 77% yield of 1-iodo-2-ethoxynaphthalene; similar results were obtained with several 1-iodo-5,5-disubstituted hydantoins.[1,4a] Few other data can be found in the literature dealing with nuclear iodinations by means of N-iodoamides or -imides.[5,6]

In the present work the halogenation reactions of aromatic compounds were performed in acetone, which shows excellent solvent ability for iodohydantoins[1] and is also a satisfactory solvent for the aromatic substrates.

In iodination with DIH no hydrogen iodide is formed; therefore, contrasting with reactions using molecular

(1) Part I: R. A. Corral and O. O. Orazi, *Anales asoc. quím. Arg.*, **44**, 11 (1956); *Chem. Abstr.*, **51**, 2751 (1957) (p. 2752, line 3: for "24.8 g." read "12.8 g.").

(2) Part of the Doctoral Thesis (1962) of H. E. B. is included in this work, which was supported by a research grant from the Consejo Nacional de Investigaciones Científicas y Técnicas.

(3) Fellow of Consejo Nacional de Investigaciones Científicas y Técnicas, 1960–1962, on leave from the Universidad Nacional de Córdoba, Argentina.

(4) As reference guides, see (a) R. A. Corral and O. O. Orazi, *J. Org. Chem.*, **28**, 1100 (1963); (b) O. O. Orazi and R. A. Corral, *Anales asoc. quím. Arg.*, **42**, 139 (1954); (c) R. A. Reed, *Chem. Prod.*, 299 (1960).

(5) A. Roedig, "Methoden der Organische Chemie," 5/4, Houben-Weyl, Georg Thieme Verlag, Stuttgart, 1960, p. 580.

(6) D. Lipkin, F. B. Howard, D. Nowotny, and M. Sano, *J. Biol. Chem.*, **238**, 2249 (1963).

TABLE I

NUCLEAR IODINATION WITH 1,3-DIIODO-5,5-DIMETHYLHYDANTOIN (DIH)

Substrate	Temp., °C.	Time, hr.	Isolation procedure	Iodo deriv.	Purification.[a]	M.p., °C.	Yield, %	DMH[b] recovd., %
Aniline	0	1	A	4-Iodo	Sublim.	62.5–63	48	89 (sublim.)
N,N-Dimethylaniline	0	0.5	A	4-Iodo		77.5–78.5	89	93
Acetanilide	56	8	B	4-Iodo	EtOH	179–180	75	67 (sublim.)
Phenol	0	0.5	A[c]	2,4,6-Triiodo	Sublim.	155–157	86	99
2-Naphthol	0	1	A	1-Iodo		92–93.5	89	95
1-Methoxynaphthalene	56	6	A	4-Iodo	MeOH	55–55.5	61	91
1-Aminonaphthalene	0	0.3	A	4-Iodo-N-acetyl[d]	EtOH	196.5–197.5	10	70 (sublim.)
2-Aminonapthalene	0	0.5	A	1-Iodo-N-acetyl[d]	EtOH	161–162[e]	55	84
2-Acetylaminonaphthalene	56	8	B	1-Iodo[f]	EtOH	161–162	62	82
2-Methylindole	20	0.3	A[g]	3-Iodo	C_6H_6–hexane	83–84	93	95
3,5-Dimethylpyrazole	20	0.5	B	4-Iodo		137–138	96	100
2-Acetylamino-4-methylthiazole	20	0.5	B	5-Iodo[h]	EtOH	185–186	85	98
2-Amino-4,6-dimethylpyrimidine	56	8	B	5-Iodo[i]	EtOH	182–183	50	86 (sublim.)
2,4-Dimethyl-6-aminopyrimidine	56	8	A	5-Iodo[j]	Sublim.; H_2O	141–142	50	100 (sublim.)

[a] The data refer to crude product when no procedure and/or solvent for purification are given. [b] 5,5-Dimethylhydantoin, carrier of halogen. [c] Using 0.003 equiv. of DIH. [d] See Experimental. [e] Undepressed by mixing with the product obtained from 2-acetylaminonaphthalene. *Anal.* Calcd. for $C_{12}H_{10}INO$: I, 40.79. Found: I, 40.83. The product already described in the literature [H. Willstaedt and G. Scheiber, *Ber.*, **67**, 466 (1934)] is apparently impure with darkening at 140° and decomposition at 167°. [f] *Anal.* Calcd. for $C_{12}H_{10}INO$: I, 40.79. Found: I, 41.05. [g] The benzene extract, without the sodium sulfite washing, on concentration and dilution with hexane gave the iodo derivative. [h] *Anal.* Calcd. for $C_6H_7IN_2OS$: I, 44.99. Found: I, 44.70. Gives a negative test for positive iodine. [i] *Anal.* Calcd. for $C_6H_8IN_3$: I, 50.96. Found: I, 50.70. [j] Incompletely described in the literature (see Beilstein). *Anal.* Calcd for $C_6H_8IN_3$: I, 50.96. Found: I, 50.47. Contains no positive iodine; the n.m.r. signal of H-5 (δ = 6.12 p.p.m.) in the substrate, disappears upon iodination.

iodine, addition of bases or oxidants is not required. The halogen carrier (5,5-dimethylhydantoin) can be easily recovered in good purity and in yields generally over 80%.

The results summarized in Table I indicate that DIH is able to react with aromatic compounds very sensitive to electrophilic substitution. Hydroxy and amino derivatives of benzene are readily attacked, furnishing high yields of the iodinated products; all iodination attempts of phenol led to the 2,4,6-triiodo-derivative even with 1 equiv. of DIH under mild conditions. An attempt to halogenate the less reactive naphthalene at 56° was unsuccessful; an extremely large predominance of solvent iodination occurs as demonstrated by differential titration of positive halogen of the DIH and the generated iodoacetone.

On the basis of the above results, reactive heterocyclic compounds were tried. At least for most of the examples investigated, iodination with DIH represents the best available method taking into account the simplicity and efficiency of the procedure.

2-Acetylamino-4-methyl-5-iodothiazole is reported[7,8] with melting point values of 218 and 220°; by both the published methods and the one herein described the same substance (identified by mixture melting point and superimposable infrared spectra), melting at 185–186°, was obtained. The structure of the product was corroborated by analytical data, infrared absorption (N–H band at 3152 cm.$^{-1}$), and particularly by comparison of the n.m.r. spectra of starting material[9] and reaction product: the doublet of the 4-methyl group (δ = 2.35 p.p.m.; J = 1 c.p.s.) changes to a singlet and the H-5 multiplet (δ = 6.58 p.p.m.) disappears.

(7) I. Garreau, *Bull. soc. chim. France*, 1048 (1954).

(8) G. Travagli, *Gazz. chim. ital.*, **78**, 592 (1948).

(9) Prepared by acetylation of 2-amino-4-methylthiazole, following essentially literature directions; m.p. 135–136° (from water).

In two examples the expected iodo derivatives were not obtained in spite of the complete (1-naphthol) or very high (85% in 1-acetylaminonaphthalene) consumption of DIH; these reactions must follow a different course since the iodine content (Stepanow) of the crude products was zero or very low. Likewise 1,3-dichloro- and 1,3-dibromo-5,5-dimethylhydantoin react quantitatively with 1-naphthol but the 4-halo derivatives are not formed[10]; however, both reagents give good yields of the 4-halo-1-acetylaminonaphthalenes.[10,11]

Several facts suggest that DIH acts as an I^+ donor for the aromatic substrates.[12] Its applicability and the comparison of the reaction conditions required for different classes of compounds (Table I) indicate that the attacking species is electrophilic in nature. Furthermore, DIH does not have the tendency to participate in homolytic processes as shown by its inability to iodinate the side chain of toluene or diphenylmethane in the presence of dibenzoyl peroxide. In this connection, it is interesting to recall that the analogous bromo compound, 1,3-dibromo-5,5-dimethylhydantoin, is able to act as a nuclear halogenating agent more efficiently in some examples (*e.g.*, anisole) under free-radical conditions.[13–15]

(10) O. O. Orazi, J. F. Salellas, M. E. Fondovila, R. A. Corral, N. Mercere, and E. R. Alvarez, *Anales asoc. quím. Arg.*, **40**, 61 (1952).

(11) O. O. Orazi and J. F. Salellas, *ibid.*, **38**, 188 (1950).

(12) See E. Chilov, *Bull. soc. chim. France*, 2903 (1963).

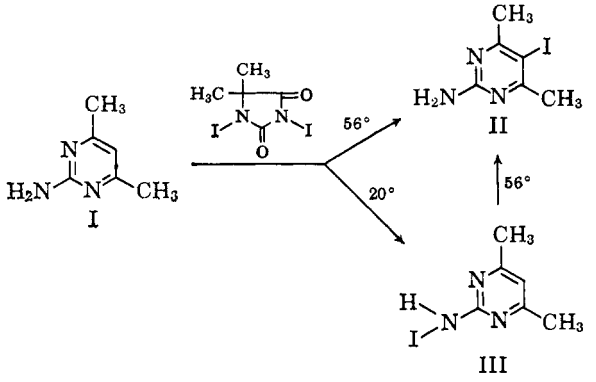
(13) J. F. Salellas, O. O. Orazi, and R. Ertola, *Anales asoc. quím. Arg.*, **38**, 181 (1950).

(14) This reaction type was studied quantitatively by K. A. Korniev and G. A. Iangol [*Dokl. Akad. Nauk SSSR*, **131**, 122 (1960)]; their conclusion regarding the relative reactivity of the bromine atoms of 1,3-dibromo-5,5-dimethylhydantoin should be reversed after our new structure [*J. Org. Chem.*, **28**, 1100 (1963)] for N-monobromo-5,5-dimethylhydantoin (1-bromo-).

(15) More recently, another example of homolytic nuclear halogenation in liquid phase using N-bromosuccinimide was described by J. R. B. Boocock and W. J. Hickinbottom, *J. Chem. Soc.*, 2587 (1961).

When studying reactions of positive-halogen transfer in hydantoins, we pointed out the tendency of the halogen to move to a center of higher electron density.[4a] According to this statement the formation of N-iodo derivatives as intermediates in the iodination of amino or acetylamino aromatic substrates could be assumed.

This expectation was shown to be correct for pyrimidine compounds. Iodination of 2-amino-4,6-dimethylpyrimidine (I) in acetone at 56° afforded the nuclear 5-iodo derivative II. When the reaction was carried out at 20° another product was isolated for which structure III is proposed.[16] Substance III, which is unstable and could not be purified, rearranges in acetone at 56° to give compound II.



The situation is best visualized as a competitive N- and C-substitution. The reaction path shown represents an alternative that, for various reasons, may not be fully realized.

With very highly reactive substances (*e.g.*, aniline) at least partial direct attack on the nucleus should be taken into account. On the other hand, the process may stop at the N-substitution stage. The N-iodo derivative[16] IV is very rapidly formed by 2,4-dimethyl-6-acetylaminopyrimidine and DIH reacting in acetone solution at 20° but no nuclear substitution occurs even at reflux temperature; attempted rearrangements of IV were unsuccessful. These results can be explained considering that the access of a iodine atom into ring position 5 is sterically hindered.

Several years ago there appeared a description of the iodination of enol acetates with N-iodosuccinimide (NIS) affording good yields of α-iodo derivatives of aldehydes and ketones; several simple representatives of these compounds were obtained advantageously, but the main usefulness resides in the selectivity of the NIS. The latter, contrasting with iodine monochloride, does not participate in additions to ethylenic linkages; taking advantage of this fact several unsaturated steroidal α-iodo ketones which are not readily accessible by other routes were prepared.[17]

On the basis of these literature data and the qualities of DIH (high iodine content, stability, and low cost) it seemed interesting to examine its behavior in this class of iodination. The results obtained in the preparation of three α-iodo ketones by the use of DIH and NIS indicate that the former possesses the same selectivity as NIS as well as equal or better halogenating ability.

(16) The iodine atom is probably on the extra-ring nitrogen since the parent amino- and acetylaminopyrimidines occur largely as such [A. R. Katritzky, *Quart. Rev.* (London), **13**, 369 (1959)].

(17) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3493 (1953); C. Djerassi, J. Grossman, and G. H. Thomas, *ibid.*, **77**, 3826 (1955).

Experimental[18]

The **1,3-diiodo-5,5-dimethylhydantoin (DIH)** was obtained through a slight modification of the earlier procedure[1]: 0.05 mole (6.4 g.) of 5,5-dimethylhydantoin and 0.1 mole (4 g.) of sodium hydroxide were dissolved in 50 ml. of cold water and mixed with 50 g. of ice; to this mixture maintained in an ice bath, a solution of 0.11 mole (18 g.) of iodine monochloride in 50 ml. of carbon tetrachloride was added dropwise while stirring magnetically. After stirring 15 min. more, the product was filtered off, washed with ice-cold water and then anhydrous ethyl acetate, and dried at 60° (under vacuum). This crude material (yield and positive iodine content, *ca.* 75 and 65%, respectively) was used without recrystallization, having been stored in a dessicator in the dark. The N-iodosuccinimide (NIS) prepared and purified (from dioxane–carbon tetrachloride) according to the literature,[17] melted at 198–200° and contained 56% of positive iodine.

The reactions were carried out using purified and anhydrous acetone and dioxane as solvents; precautions to exclude light and humidity were taken. The consumption of the halogenating agent was followed by iodometric titration in acetic–acetate buffer medium[19]; under these conditions, no iodine is generated from the α-iodo ketones formed with acetone or enol acetates. The reaction was stopped when the consumption was completed or remained unchanged.

Nuclear Iodination (see Table I).—The substrate (0.001 mole) was dissolved at the reaction temperature in the required volume (2–5 ml.) of acetone and, then, the amount of DIH containing 0.001 g.-atom of iodine was added. For very reactive substrates this addition of DIH was made portionwise (magnetic stirring) either as solid or in acetone solution.

At the end of the reaction, the solvent was distilled off under reduced pressure and the residue was subjected to one of the following procedures.

Method A.—Repeated extractions with benzene left an insoluble material that, directly or after vacuum sublimation at 60–100° (1–5 μ), was identified as 5,5-dimethylhydantoin by melting point and mixture melting point. The benzene extract was washed with a dilute aqueous solution of sodium sulfite and then with water and was dried with magnesium sulfate; removal of the solvent under reduced pressure furnished the crude iodinated product.

Method B.—The aqueous extract obtained from the residue was evaporated to dryness giving the 5,5-dimethylhydantoin identified as above. The unextracted material washed with sodium sulfite and water and dried *in vacuo* provided the crude iodo derivative.

In some examples the iodo compounds thus obtained were pure. In other cases they were purified by crystallization or vacuum sublimation. Generally the identification was made by mixture melting points with authentic samples prepared according to literature methods; when the reference substances were not readily accessible, the identification rested on coincidence with literature melting point values and iodine analyses.

Because of instability, iodonaphthylamines were isolated as N-acetyl derivatives: the crude product was heated with excess of acetic anhydride for 15 min. at 80° and the reaction mixture was evaporated to dryness *in vacuo;* the chloroform extract of the residue, washed with water and dried, furnished the iodo derivatives of acetylaminonaphthalenes upon removal of the solvent. These compounds were purified by crystallization from alcohol, preceded for the 1-acetylamino-4-iodo isomer by chromatography on alumina (Woelm, alkaline, activity I, and benzene–ethyl ether mixtures as eluent).

2-(Iodoamino)-4,6-dimethylpyrimidine (III).—Acetone solutions of 0.001 mole (0.123 g.) of 2-amino-4,6-dimethylpyrimidine in 2 ml. and 0.001 equiv. (0.198 g.) of DIH in 1.5 ml. were mixed at room temperature; immediate separation of the product was facilitated by scratching the vessel.

After some hours in the refrigerator, the insoluble portion was centrifuged, washed (magnetic stirring) with 1 ml. of acetone, and

(18) Melting points are not corrected and, unless specified, were taken in capillaries. The n.m.r. spectra (in deuteriochloroform solution with tetramethylsilane as internal standard) were recorded and electronically integrated with a Varian A-60 spectrometer; the infrared spectra were taken in Nujol mulls using a prism-grating instrument (Perkin-Elmer Model 221). The microanalyses indicated in Table I were performed by Dr. A. Bernhardt, Mülheim, Germany.

(19) E. D. Hughes, H. B. Watson, and E. D. Yates, *J. Chem. Soc.*; 3318 (1931).

dried at 42° (40 μ) to constant weight; 0.146 g. (59%) of III was obtained containing 49% of positive iodine (calcd. for $C_6H_8IN_3$: I, 50.96). Purification attempts did not succeed. Compound III is an amber solid that darkens after few days at room temperature.

Products from different experiments contained between 43 and 49% of positive iodine.

Compound III (60 mg.) was heated in 2 ml. of acetone at 56° for 8 hr. in the dark; removal of the solvent gave a solid which contained only 3% of positive iodine. This material, after washing with sodium sulfite solution and water, was crystallized from alcohol; 30 mg. (50%) of 2-amino-4,6-dimethyl-5-iodopyrimidine (II) was obtained and identified by melting point and mixture melting point and by comparison of the infrared absorption spectra with the sample prepared as indicated in Table I.

2,4-Dimethyl-6-(N-iodo-N-acetylamino)pyrimidine (IV).—The starting material, 2,4-dimethyl-6-acetylaminopyrimidine, was dried at 56° (25 mm.) to constant weight to remove the water of crystallization; reaction as above resulted in 50% yield of IV as an almost white solid that decomposes on standing at room temperature, m.p. 156–158° dec.

Anal. Calcd. for $C_8H_{10}IN_3O$: I, 43.61. Found: positive I, 42.8.

Treatment of 25 mg. of IV with aqueous sodium sulfite solution followed by evaporation and sublimation at 100° (0.1 mm.) provided 14 mg. of 2,4-dimethyl-6-acetylaminopyrimidine which, upon crystallization from water, melted at 181–183° and was identified by mixture melting point and infrared absorption.

By heating IV for 8 hr. in boiling acetone, with or without 1 equiv. of 2,4-dimethyl-6-acetylaminopyrimidine, a very low disappearance of positive iodine occurred. Similar results were obtained in the same manner with stoichiometric amounts of 2,4-dimethyl-6-acetylaminopyrimidine and DIH.

Preparation of α-Iodo Ketones.—The enol acetates, prepared following literature procedures, were iodinated essentially as described[17] using NIS. The positive halogen of α-iodo ketones was analyzed iodometrically in aqueous acetone acidified with sulfuric acid.

3-Iodo-2-heptanone.—To a solution of 0.025 mole of 2-hepten-2-ol acetate in 10 ml. of dioxane 0.023 equiv. of DIH were added; after magnetic stirring for 1 hr. at 90°, the solvent was removed *in vacuo* and the residue was extracted with several portions of carbon tetrachloride.

The insoluble material, m.p. 174–175° (75%), was identified by mixture melting point as 5,5-dimethylhydantoin.

Fractionation of the carbon tetrachloride extract furnished 3-iodo-2-heptanone, 76% yield, b.p. 77–80° (1.7 mm.), lit. b.p. 75° (1.5 mm.).

Anal. Calcd. for $C_7H_{13}IO$: I, 52.86. Found: I, 52.66.

Iodination with NIS afforded the 3-iodo-2-heptanone in 76% yield; reported[17] yield under the same conditions was 58%.

ω-Iodoacetophenone.—A solution of 0.001 mole of 1-phenylethen-1-ol acetate in 0.5 ml. of dioxane and 0.001 equiv. of DIH was magnetically stirred for 3 hr. at 50°; the undissolved DIH disappeared after *ca.* 2.5 hr. The solvent was distilled off under reduced pressure and the residue was extracted with benzene. The 5,5-dimethylhydantoin (87%) that remained undissolved was identified as above.

The benzene extract was heated for 1 hr. at 80° after the addition of 0.5 ml. of pyridine; the crystalline product which separated in the cold, 0.242 g. (88%), gave m.p. 197–199°, raised to 202–204° on recrystallization from water; no depression occurred by mixing with an authentic sample of phenacylpyridinium iodide melting at 202–204°.

Fractionation of the reaction products at low temperature using carbon tetrachloride instead of benzene left an insoluble material which, recrystallized from ethyl acetate, provided 22 mg. (21% yield) of crystals, m.p. 123–127°. The latter, on the basis of infrared spectral comparison, was identical with the monoacetyl derivative of 5,5-dimethylhydantoin preferably described[4a,20] as 2-enol-5,5-dimethylhydantoin acetate.

Working in the same fashion, but using NIS, the reaction was not completed, 37% of the halogenating agent (55.3% positive iodine) being recovered. The pyridinium salt (55%), after recrystallization from water, melted at 203–205°.

3-β-Acetoxy-21-iodo-Δ⁵-pregnen-20-one.—The reaction was carried out as described in the literature using NIS.[17] The iodo ketone, purified from methanol–water (56% yield), gave m.p. 139–141° (Kofler micro hot stage) and was identical, according to mixture melting point and infrared absorption, with an authentic specimen obtained in same yield using NIS.

Anal. Calcd. for $C_{23}H_{33}IO_3$: I, 26.19. Found: I, 26.40.

(20) M. R. Salmon and A. Z. Kozlowki, *J. Am. Chem. Soc.*, **67**, 2270 (1945).

The Structures of the Isoisatogens[1,2]

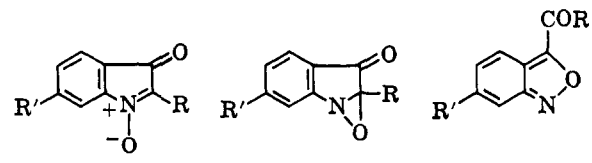
JACK L. PINKUS,[3a,4] GORDON G. WOODYARD,[3b] AND THEODORE COHEN[3a]

Departments of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, and Wheeling College, Wheeling, West Virginia

Received November 5, 1964

The acid-catalyzed isomerization of isatogens (1) into isoisatogens is shown to give 3-aroylanthranils (3) and not oxaziranes (2) as suggested by Ruggli.

During their extensive studies into the chemistry of nitrogen heterocycles,[5] Ruggli and co-workers investigated the acid-catalyzed isomerization of the bright orange-red isatogens (1) into pale yellow isomers which were called isoisatogens and were formulated as the corresponding oxaziranes (2).[6–12] The reactions were generally carried out in an alcohol solvent at steam-bath temperatures in a pressure vessel employing hydrogen chloride or sulfuric acid as the catalyst. Under



1a-g 2a-e 3a-e

a, R = C_6H_5; R′ = NO_2
b, R = C_6H_5; R′ = $CO_2C_2H_5$
c, R = $C_6H_2NO_2Cl_2$; R′ = H
d, R = C_6H_5; R′ = H
e, R = C_5H_4N; R′ = H
f, R = CO_2CH_3; R′ = H
g, R = $CO_2C_2H_5$; R′ = H

(1) This work was supported by a research grant (CA-06912) to Wheeling College from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) A portion of this work was reported in a preliminary communication: see J. L. Pinkus, T. Cohen, M. Sundaralingam, and G. A. Jeffrey, *Proc. Chem. Soc.*, 70 (1960).

(3) (a) Department of Chemistry, University of Pittsburgh; (b) Department of Chemistry, Wheeling College.

(4) To whom inquiries should be addressed.

(5) For a complete listing of P. Ruggli's publications, see H. Rupe, *Helv. Chim. Acta*, **24**, 796 (1946).

(6) P. Ruggli, *Ber.*, **52**, 1 (1919).

(7) P. Ruggli and A. Bolliger, *Helv. Chim. Acta*, **4**, 626 (1921).

(8) P. Ruggli and A. Bolliger, *ibid.*, **4**, 637 (1921).

(9) P. Ruggli, A. Bolliger, and W. Leonhardt, *ibid.*, **6**, 594 (1923).

(10) P. Ruggli and H. Zaeslin, *ibid.*, **22**, 134 (1939).

(11) P. Ruggli, E. Caspar, and B. Hegedüs, *ibid.*, **22**, 140 (1939).

(12) P. Ruggli and H. Cuenin, *ibid.*, **27**, 649 (1944).