moved slower than the parent compound (X). The analytical data are given in Table III.

Infrared spectrum: λ_{max}^{KBr} 3.3–3.4, 6.12, and 6.80 ($\overset{+}{N}H_3$); 6.27 (shoulder) and 7.25 (CO_2^-); 9.82 (S → 0); 13.25μ (*m*-disubstituted phenyl).

*S-Carboxymethyl-*L*-cysteine sulfone* (XXX). *Method L.* A mixture of 1.0 g. (5.6 mmoles) of recrystallized *S*-carboxymethyl-L-cysteine (I), 5 ml. of water, and 5 ml. (48 mmoles) of 30% hydrogen peroxide was heated at 45–60°, with occasional stirring, for 10 hr. A small amount of material remained in suspension at the end of this time and was removed by filtration. To the filtrate was added about 0.2 g. of 5% platinum-on-charcoal catalyst (Baker and Co.) in small portions; the vigorous reaction required cooling. A copious, white precipitate formed during this treatment. The precipitate was brought into solution with 100 ml. of hot (80°) water and the resulting mixture was filtered to remove the platinum catalyst. The filtrate was evaporated *in vacuo*, leaving a yellow solid. This was crystallized from 40 ml. of water, using decolorizing carbon, to give 0.3 g. of white material that crystallized very slowly. This amounted to a 25% yield but no effort was made to recover the product which remained in the mother liquors. The material was crystallized a second time from 25 ml. of hot water. It melted at 193–194° (dec.)[22] and gave a single red-brown spot on paper chromatography in solvent system A which moved faster than the sulfoxide XXIV and slower than the parent compound (I). The analytical data are given in Table IV.

Infrared spectrum: λ_{max}^{KBr} 3.35, 6.04, and 6.57 ($\overset{+}{N}H_3$); 5.79 (carboxyl C = O); 6.35 and 7.08 (CO_2^-), 7.70 and 8.83μ (SO_2).

*S-4-Nitrophenyl-*DL*-cysteine sulfone* (XXXVI). *Method M.* A solution of 0.50 g. (2.1 mmoles) of *S*-4-nitrophenyl-DL-cysteine (XIII) in 10 ml. of water, 2.5 ml. of 6*N* hydrochloric acid, and 1.50 ml. (14.7 mmoles) of 30% hydrogen peroxide was heated on the steam bath for 10 min. A small amount of an unidentified precipitate was filtered and the filtrate was heated for an additional 80 min. The solution was chilled and adjusted to *p*H 6–7 with concentrated ammonium hydroxide. A precipitate, 0.40 g. (70%) slowly formed and was recrystallized from water (1 g./20 ml.), m.p. 156–157° dec. The product gave a single light yellow spot on paper chromatography in solvent system C which moved slower than the parent compound (XIII). The analytical data are given in Table IV.

Infrared spectrum: $\lambda_{max\mu}^{KBr}$ 3.23–3.45, 6.08, and 6.76 (shoulder) ($\overset{+}{N}H_3$); 6.35 and 7.15 (shoulder) (CO_2^-); 6.52 and 7.40 (NO_2); 7.68 and 8.70 (SO_2); 12.05 (*p*-disubstituted phenyl).

*S-4-Fluorophenyl-*L*-cysteine sulfone* (XXXVIII). *Method N.* To a solution of 1.0 g. (4.64 mmoles) of S-4-fluorophenyl-L-cysteine (XVI) in 20 ml. of glacial acetic acid was added 5.0 ml. (49 mmoles) of 30% hydrogen peroxide. The resulting solution was allowed to stand at room temperature for 49 hr. after which the excess hydrogen peroxide was decomposed by the addition of about 0.2 g. of 5% platinum-on-charcoal catalyst, added in small portions. The charcoal was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of water and the resulting solution was neutralized to *p*H 7 with concentrated ammonium hydroxide yielding 0.80 g. (70%) of crystalline solid. This was recrystallized from hot water (0.2 g./25 ml.) to yield 0.60 g. (52%) of product, m.p. 172–174° (dec.). The product gave a single yellow spot on paper chromatography in solvent system C which moved slower than the parent amino acid (XVI). The analytical data are given in Table IV.

Infrared spectrum: $\lambda_{max\mu}^{KBr}$ 3.37–3.45, 6.05–6.10, and 6.60 ($\overset{+}{N}H_3$); 6.30 and 7.15 (CO_2^-); 7.60 and 8.72 (SO_2); 8.06 (C—F); 11.87 (*p*-disubstituted phenyl).

Acknowledgements. The authors wish to thank Dr. Peter Lim for infrared interpretations, Dr. L. K. Moss and group for column and paper chromatography, and Mr. O. P. Crews, Jr., and group for the large-scale preparation of intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] VI. Synthesis of α-Amino-γ-sulfamoylbutyric Acids with Substituents on the Sulfonamide Nitrogen

CAROL W. MOSHER, R. M. SILVERSTEIN, OSBORNE P. CREWS, JR., AND B. R. BAKER

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Chlorinolysis of L-cystine hydantoin and DL-homocystine hydantoin in 42% aqueous acetic acid gave 71% and 81% yields, respectively, of the corresponding 5-(chlorosulfonylalkyl)hydantoins. Procedures were devised for reaction of DL-5-(β-chlorosulfonylethyl)hydantoin with ammonia, alkylamines, arylamines, and glycinamide to form the respective sulfonamides, which, in turn, were base-hydrolyzed to the desired DL-α-amino-γ-sulfamoylbutyric acids. In contrast, L-5-(chlorosulfonylmethyl)hydantoin reacted satisfactorily only with the arylamines, and the resultant sulfonamides decomposed on attempted alkaline hydrolysis.

Interest in antagonists of L-glutamine as possible anticancer agents has been given considerable impetus by the observed anticancer activity of L-azaserine[2] and 6-diazo-5-oxo-L-norleucine.[3] These two compounds have been established to be antimetabolites of L-glutamine.[4] Reisner[5] has recently described the synthesis of α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$) along with two

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper in this series, *cf.* L. Goodman, L. O. Ross, and B. R. Baker, *J. Org. Chem.*, **23**, 1251 (1958).

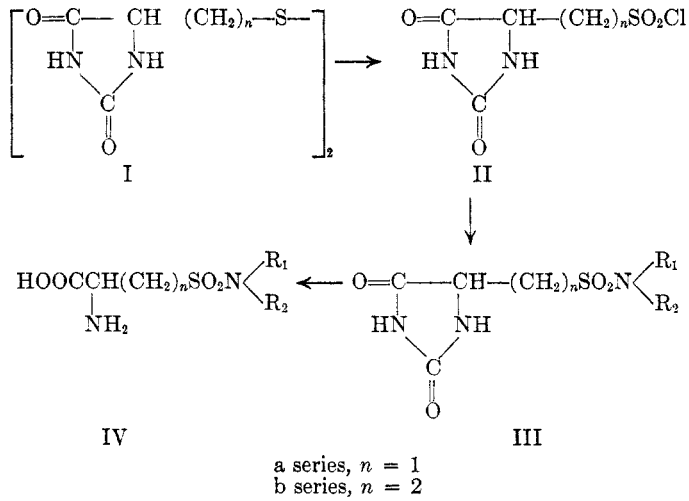
(2) C. C. Stock, H. C. Reilly, S. M. Buckley, D. A. Clarke, and C. P. Rhoads, *Nature*, **173**, 71 (1954).

(3) H. A. DeWald and A. M. Moore, Abstracts, American Chemical Society, 129th Meeting, 13 M (1956).

(4) B. Levenberg, I. Melnick, and J. M. Buchanan, *J. Biol. Chem.*, **225**, 163 (1957).

(5) D. B. Reisner, *J. Am. Chem. Soc.*, **78**, 5102 (1956).

related compounds, α-amino-γ-(ethylsulfamoyl)-butyric acid (IVb, $R_1 = C_2H_5$, $R_2 = H$) and α-amino-γ-[2-(benzylthio)ethylsulfamoyl)-butyric acid (IVb, $R_1 = C_6H_5CH_2SCH_2CH_2$, $R_2 = H$). Since he showed that α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$) had activity against T_2 coliphage of *E. coli* that was reversible by either glutamic acid or glutamine and since this amino acid had presumably not been tested as an anticancer agent,[6] the synthesis was repeated to obtain material for antitumor evaluation; several improvements in the procedures have given higher yields. In addition, a wider spectrum of substituents on the sulfonamide nitrogen has been investigated.



Chlorinolysis of DL-homocystine hydantoin (Ib) in aqueous suspension as described by Reisner[5] gave low and variable yields of pure DL-5-(β-chlorosulfonylethyl)hydantoin (IIb), particularly on a large scale. The main difficulty was that an insoluble, gummy mixture of product and starting material formed frequently and did not react further. It has now been found that 42% aqueous acetic acid is an excellent solvent for this reaction; since the product, but not the starting material, is soluble, total solution indicates completion of reaction. Consistent yields of better than 80% of nearly analytically pure material were obtained by this modification.

Treatment of an ether suspension of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) with ammonia as previously described[5] gave only a 20% yield of DL-5-(β-sulfamoylethyl)hydantoin (IIIb, $R_1 = R_2 = H$). Reisner recorded[5] a yield of 40% under these conditions. Again, since neither the starting acid chloride nor the products were soluble in ether, incomplete reaction resulted. In contrast, the use of the excellent solvent *N*,*N*-dimethylformamide gave a 62% yield of pure sulfonamide (IIIb, $R_1 = R_2 = H$). Hydrolysis[5] of the hydantoin moiety by aqueous barium hydroxide at 160° gave a 73% yield of pure DL-α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$). Thus, with the above improvements the over-all yield from DL-homocystine hydantoin (Ib)[7] was increased more than one-and-a-half-fold from the previously described[5] yield of 21%.

Similarly, morpholine and diethylamine reacted with DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in *N*,*N*-dimethylformamide to give the corresponding new sulfonamides (IIIb) in 76% and 55% yield, respectively (Procedure A, Table I.) Hydrolysis[5] with barium hydroxide at 160° afforded good yields of the corresponding amino acids (IVb) (Table II).

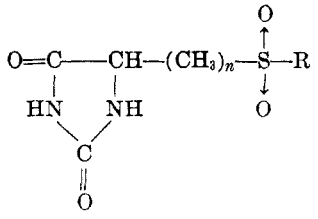
Attempts to react DL-5-(β-chlorosulfonylethyl)-hydantoin (IIb) with glycine ethyl ester hydrochloride in *N*,*N*-dimethylformamide containing triethylamine failed to give any of the desired *N*-(carbethoxymethyl)sulfonamide (IIIb, $R_1 = CH_2CO_2C_2H_5$, $R_2 = H$). With the more stable glycinamide hydrochloride under these conditions, a 50% yield of the desired sulfonamide (IIIb, $R_1 = CH_2CONH_2$, $R_2 = H$) was obtained. Hydrolysis with barium hydroxide at 160° followed by crystallization from water at *p*H 3 gave the peptide analog of γ-glutamylglycine, namely, DL-α-amino-γ-(*N*-carboxymethylsulfamoyl)butyric acid (IVb, $R_1 = CH_2COOH$, $R_2 = H$). A hydantoinsulfonamide (IIIb) could be obtained from phenylhydrazine in good yield, but the hydrolysis with barium hydroxide gave deep-seated decomposition, as indicated by the absence of sulfonamido S→O bands in the infrared absorption spectrum of the corresponding amino acid fraction; this reaction was not investigated further.

Although *N*,*N*-dimethylformamide was satisfactory for the preparation of the sulfonamides (IIIb) derived from aliphatic amines, the procedure worked poorly with arylamines. However, the use of pyridine as a solvent (Procedure B) gave sulfonamides (IIIb) derived from aniline in 35%

(6) We wish to thank Dr. Howard W. Bond of the Cancer Chemotherapy National Service Center and Dr. Ralph K. Barclay of the Sloan-Kettering Institute for Cancer Research for this information.

(7) J. V. Karabinos and J. L. Szabo, *J. Am. Chem. Soc.*, 66, 649 (1944).

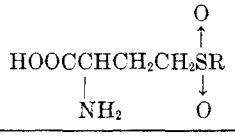
TABLE I



R[a]	n	Yield, %	Procedure	M.P., °C.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Et_2N—	2	55	A	111–113 d.[b]	41.1	6.50	16.0	41.4	6.46	15.7
Morpholino	2	76	A	162–165[c]	39.0	5.45	15.2[d]	39.2	5.25	14.7
C_6H_5NH—	2	86	C[f]	207–209[e]	46.6	4.63	14.8[e]	46.5	4.73	14.8
C_6H_5NHNH—	2	84	C[m]	168–172 d.[f]	44.3	4.73	18.8	43.9	4.67	18.5
p-Cl-C_6H_4NH—	2	80	C[g]	196–198[h]	41.6	3.81	13.2[i]	41.7	3.74	13.3
m-CF_3-C_6H_4NH—	2	74	C[k]	188–189[f]	41.0	3.44	12.0[l]	41.0	3.36	11.9
3,4-Me_2-C_6H_3NH—	2	69	C	194–197[c]	50.2	5.47	13.5	50.2	5.68	13.8
p-F-C_6H_4NH[n]	2	69	C	211–213 d.[o]	43.9	4.01	14.0	43.9	4.10	13.7
p-F-C_6H_4NH[n]	2	75	C	170–173 d.[c]	43.9	4.01	14.0	44.1	4.40	14.0
m-Cl-C_6H_4NH—	2	84	C	206–207[c]	41.6	3.81	13.2	41.6	4.02	12.9
3,4-Cl_2-C_6H_4NH—	2	77	C	218–220[h]	37.5	3.15	11.9	37.6	3.27	11.5
p-Cl-C_6H_4NH—	1	68	C	203–207 d.[h]	39.5	3.32	13.8	39.6	3.46	13.6
m-CF_3-C_6H_4NH—	1	50	C	143–152 d.[c]	39.2	2.99	12.5	39.1	3.11	12.5

[a] All compounds had characteristic infrared absorption bands for the two hydantoin carbonyls and for the S → O vibration of the sulfonamide group. Compounds with $n = 2$ were DL-isomers and with $n = 1$ were L-isomers. [b] Recrystallized from methylene chloride–petroleum ether (b.p. 30–60°). [c] Recrystallized from H_2O. [d] Calcd. for S, 11.6. Found: S, 11.4. [e] Calcd. for S, 11.3. Found: S, 11.3. [f] Recrystallized from absolute ethanol. [g] Procedure B gave a 57% yield. No product could be isolated by Procedure A. [h] Recrystallized from 50% ethanol. [i] Calcd. for S, 10.1; Cl, 11.2. Found: S, 9.96; Cl, 11.1. [j] Procedures A and B gave 35% yields. [k] Procedure B gave a 48% yield. [l] Calcd. for S, 9.13. Found: S, 8.98, 9.02. [m] Procedure A gave a 76% yield. [n] Two crystal forms were obtained which were interconvertible by proper seeding. [o] Recrystallized from 70% ethanol.

TABLE II



R[a]	Yield, %	M.P. °C., dec.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
NH_2—	73[b]	232[c,d]			15.4			15.6
Et_2N—	87	205–210[e]	40.3	7.61	11.8	40.0	7.62	11.6
Morpholino	70	235–237[d]	38.1	6.39	11.1	38.5	6.30	11.4
C_6H_5NH—	58	238–240[d]	46.5	5.46	10.9[h]	46.3	5.47	10.7
p-Cl-C_6H_4NH—	37	235–243[d]	41.0	4.48	9.57	41.1	4.62	9.66
m-CF_3-C_6H_4NH—	56	228–234[d]	40.5	4.02	8.59	40.7	4.21	8.52
$HOOCCH_2NH$—	60	214–220[f,g]	30.0	5.04	11.2	30.0	5.07	11.4
3,4-Me_2-C_6H_3NH—	69	226–228[d]	50.2	6.32	9.80	50.1	6.32	9.72

[a] All compounds were prepared by barium hydroxide hydrolysis of the corresponding hydantoin at 160° according to the method of Reisner.[5] All the compounds showed infrared bands typical of the zwitterion structure of an α-amino acid and also showed typical S → O bands of a sulfonamide. [b] Reisner[5] reported a yield of 53%, m.p. 247° dec. [c] This compound gave a single spot, detected by ninhydrin, on Whatman No. 1 paper with either *t*-BuOH/HCOOH/H_2O (70/10/30) or methyl Cellosolve/H_2O (9/1). [d] Recrystallized from water. [e] Recrystallized from water by addition of 12 volumes of ethanol. [f] Recrystallized from 80% ethanol. [g] In addition to showing the typical bands exhibited in the infrared by these amino acids, this compound showed carboxyl absorption at 5.81μ. The usual work-up[5] of this compound afforded the ammonium salt of the desired product. The free acid crystallized from water at *p*H 3. [h] Calcd. for S, 12.4. Found: S, 12.3.

yield, *p*-chloroaniline in 57% yield, and *m*-(trifluoromethyl)aniline in 48% yield. Much higher yields of the sulfonamides (IIIb) (74–80%) were obtained when the sulfonyl chloride was added portionwise to an ethanolic solution of two equivalents of aromatic amine (Procedure C). Hydrolysis with barium hydroxide to the corresponding amino acids containing an *N*-arylsulfonamide group proceeded satisfactorily (Table II).

Addition of aqueous sodium azide to the sulfonyl chloride (IIb) in alcohol gave a 56% yield of the corresponding sulfonyl azide. However, attempted hydrolysis of the hydantoin ring with barium hydroxide gave deep-seated decomposition as de-

tected by lack of S→O bands of the sulfonamide in the infrared spectrum of the amino acid fraction.

The lower homologous members of this series derived from L-cystine hydantoin (Ia)[8] were also investigated. Chlorinolysis of L-cystine hydantoin (Ia) in aqueous suspension was completely unsuccessful, possibly due to either the insolubility of the starting material or the instability of the product or both. In contrast, chlorinolysis in 42% aqueous acetic acid gave a 71% yield of L-5-(chlorosulfonylmethyl)hydantoin (IIa). This compound was somewhat unstable; after a few days the odor of sulfur dioxide was present and in a few weeks the compound had decomposed, presumably by β-elimination of the chlorosulfonyl group.

L-5-(Chlorosulfonylmethyl)hydantoin (IIa) failed to give any sulfonamide (IIIa) when its solution in *N,N*-dimethylformamide was treated with ammonia. The crude product showed the proper absorption bands in the infrared for the hydantoin ring, but no S→O bands of a sulfonamide. Similarly, the sulfonyl chloride IIa gave no detectable sulfonamide when added to ethanolic ammonia. The product isolated contained typical hydantoin carbonyl bands in the infrared, but no sulfonamide S→O bands.

When L-5-(chlorosulfonylmethyl)hydantoin (IIa) was added portionwise to a solution of two equivalents of *p*-chloroaniline or *m*-(trifluoromethyl)-aniline in ethanol (Procedure C), satisfactory conversion (68% and 50%, respectively) to the desired *N*-arylsulfonamides (IIIa) was obtained. Attempts to hydrolyze either of these L-5-(sulfamoylmethyl)hydantoins (IIIa) with barium hydroxide to the respective α-amino acids (IVa) led to complete breakdown of the molecule, presumably initiated by β-elimination of the sulfonamide residue.[9]

EXPERIMENTAL[10]

DL-5-(*β-Chlorosulfonylethyl*)*hydantoin* (IIb). Chlorine gas was bubbled through a stirred suspension of 73 g. (0.23 mole) of DL-homocystine hydantoin (Ib)[7] in 750 ml. of water and 560 ml. of glacial acetic acid until complete solution was effected (1–3 hr.). The temperature was maintained at 15–20° by adequate cooling. The solution was poured into 1.4 l. of cold water, then saturated with salt and extracted with ethyl acetate (4 × 350 ml.). The combined extracts were dried with magnesium sulfate,[11] then evaporated to dryness *in vacuo* (bath 50°). The residue was dissolved in 700 ml. of hot ethyl acetate and filtered from a little insoluble material. Dilution with 1200 ml. of petroleum ether (b.p. 30–60°) and chilling gave 85.7 g. (81%) of nearly pure material, m.p. 138–139° dec.; λ_{max}^{Nujol} 3.10μ (NH), 5.68μ (C_4=O of hydantoin), 5.82μ (C_2=O of hydantoin), 7.54, 8.67μ (S → O of SO_2Cl).

Reisner[5] has recorded a crude yield (m.p. 122–124°) of 88% by chlorinolysis in water; the yield of pure material, m.p. 141–142° dec., was not recorded.

The rate of chlorination is dependent upon the type of stirring. With very rapid stirring and high rate of passage of chlorine, solution can be completed in 15 min. The chlorination should be stopped as soon as solution is complete, since further reaction leads to 5-(β-chlorosulfonylethyl)-1,3-dichlorohydantoin, m.p. 134–135°. A mixture of the latter with 5-(β-chlorosulfonylethyl)hydantoin melted about 115–120°.

Anal. Calcd. for $C_5H_5Cl_2N_2O_4S$: C, 20.3; H, 1.70. Found: C, 20.7; H, 2.12.

This compound contains positive chlorine, as shown by a potassium iodide test, and can be reconverted to the desired product by treatment with sodium bisulfite in dilute acetic acid. The *N*-chloro derivative can also be differentiated from the desired product by the difference in NH absorption at about 3μ and the hypsochromic shift of the hydantoin carbonyls of about 0.1μ.

L-5-(*Chlorosulfonylmethyl*)*hydantoin* (IIa). Chlorinolysis of 10 g. (0.034 mole) of L-cystine hydantoin (Ia)[8] in 75 ml. of acetic acid and 100 ml. of water, as described in the preceding experiment, gave 13.8 g. of residue, m.p. 137–142° dec., on evaporation of the ethyl acetate extracts. Recrystallization from 130 ml. of ethyl acetate by the addition of petroleum ether (b.p. 30–60°) gave 9.17 g. (62%) of pure product, m.p. 149–151° dec.; λ_{max}^{Nujol} 3.10, 3.20, 3.30μ (NH), 5.62μ (C_4=O of hydantoin), 5.74μ (C_2=O of hydantoin), 7.27, 8.41, 8.67μ (S → O of —SO_2Cl).

Anal. Calcd. for $C_4H_5ClN_2O_4S$: Cl, 16.7. Found: Cl, 16.8.

In a larger run the yield of crude product was 60 g. (71%) in two crops, m.p. 143–146° dec. and 139–141° dec.

DL-5-(*β-Sulfamoylethyl*)*hydantoin* (IIIb, $R_1 = R_2 = H$). Ammonia was passed for 75 min. through a stirred solution of 4.52 g. (0.02 mole) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 15 ml. of dry *N,N*-dimethylformamide cooled in an ice bath. The solvent was evaporated *in vacuo*. Recrystallization from 12 ml. of water with the aid of Norit gave 2.46 g. of product, m.p. 183–185°. By concentration of the mother liquor *in vacuo*, an additional 0.18 g. (total 62%), m.p. 184–185°, was obtained. Recrystallization of a sample from water gave white crystals, m.p. 186.5–187°; λ_{max}^{KBr} 3.10μ (NH), 5.68μ (C_4=O of hydantoin), 5.85μ (C_2=O of hydantoin), 6.50μ (NH of SO_2NH), 7.62, 8.82μ (S → O of SO_2NH).

Anal. Calcd. for $C_5H_9N_3O_4S$: C, 29.0; H, 4.38. Found: C, 29.0, 29.1; H, 4.40, 4.50.

The use of ether for the solvent as recommended by Reisner[5] gave a 20% yield of impure product, m.p. 169–178°. He recorded[5] a yield of 40% and m.p. of 182–183°.

Attempts to prepare 5-(sulfamoylmethyl)hydantoin by this procedure or with ethanol as the solvent were unsuccessful.

DL-5-(*β-Diethylsulfamoylethyl*)*hydantoin* (IIIb, $R_1 = R_2 = C_2H_5$). *Procedure A.* To a stirred solution of 1.81 g. (8 mmoles) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 5 ml. of dry *N,N*-dimethylformamide cooled in an ice bath was added dropwise 2.19 g. (30 mmoles) of diethylamine. After being stirred in the cooling bath for an additional 75 min., the mixture was allowed to stand at 3° for about 16 hr. in a stoppered flask. The precipitate of diethylamine hydrochloride was removed by filtration and washed with 2 ml. of *N,N*-dimethylformamide. The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was crystallized from water. For further details, see Table I. Other compounds prepared by this method (Procedure A) are also listed in Table I.

DL-5-[*β-(p-Chlorophenylsulfamoyl)ethyl*]*hydantoin* (IIIb, R_1 = *p*-Cl-C_6H_4, R_2 = H). *Procedure B.* To a stirred solution of 1.13 g. (5 mmoles) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 7 ml. of reagent pyridine was added a solution

(8) W. C. Hess, *J. Am. Chem. Soc.*, **56**, 1421 (1934).

(9) The ability of sulfur functions β to a carboxyl to eliminate is well known. For example, cystine and cysteine and cysteic acid are unstable to base. *Cf.* also B. R. Baker, M. V. Querry, W. L. McEwen, S. Bernstein, S. R. Safir, L. Dorfman, and Y. SubbaRow, *J. Org. Chem.*, **12**, 186 (1947).

(10) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(11) The process must be carried to this point without interruption, otherwise a lowering of the yield occurs.

of 0.64 g. (5 mmoles) of *p*-chloroaniline in 5 ml. of pyridine. After 30 min., the solvent was removed *in vacuo* and the residue crystallized from 55 ml. of water with the aid of Norit; yield, 0.90 g. (57%), m.p. 190–191°. Recrystallization from 50% ethanol gave white crystals, m.p. 196–198°; λ_{max}^{KBr} 2.93, 3.10, 6.70μ (NH), 5.65μ (C_4=O of hydantoin), 5.82μ (C_2=O of hydantoin), 7.55, 8.75μ (S → O of —SO_2N—), 11.95μ (*p*-disubstituted phenyl). For additional details and for other compounds prepared in the manner (Procedure B), see Table I.

DL-5-(*β-Phenylsulfamoylethyl*)*hydantoin* (IIIb, R_1 = C_6H_5, R_2 = H). *Procedure C.* To a stirred solution of 15.8 g. (0.17 mole) of aniline in 120 ml. of 95% ethanol was added portionwise 20.0 g. (0.088 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) over a period of 5 min. The reaction mixture was stirred for 90 min., then was allowed to stand overnight. The product was collected on a filter and washed with 40 ml. of 95% ethanol; yield, 20.7 g. (86%), m.p. 205–207°. For additional details, see Table I. Other compounds prepared by this method (Procedure C) are described in Table I. In some cases it was necessary to evaporate the ethanol and crystallize the product from water.

DL-5-[(*β-Carbamoylmethylsulfamoyl*)*ethyl*]*hydantoin* (IIIb, R_1 = CH_2CONH_2, R_2 = H). To a warm (56°) mixture of 0.90 g. (8.1 mmoles) of glycinamide hydrochloride in 8 ml. of dry *N,N*-dimethylformamide and 5 ml. of dry triethylamine was added with stirring a solution of 1.81 g. (8 mmoles) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 5 ml. of *N,N*-dimethylformamide, the temperature rising to 71°. After being stirred for an additional 45 min., the heterogeneous mixture was allowed to stand for 20 hr. in a closed flask. The reaction mixture was processed as in Procedure A; yield, 1.05 g. (50%), m.p. 230–248° dec. Two recrystallizations from 95% ethanol gave white crystals with the same m.p.; λ_{max}^{KBr} 2.88, 2.99, 3.12μ (NH), 5.66μ (C_4=O of hydantoin), 5.80μ (C_2=O of hydantoin), 6.00μ (amide C=O), 7.55, 8.75μ (S → O of —SO_2N—).

Anal. Calcd. for $C_7H_{12}N_4O_5S$: C, 31.8; H, 4.57; N, 21.2. Found: C, 32.1; H, 4.50; N, 20.8.

DL-5-(*β-Azidosulfonylethyl*)*hydantoin.* To a stirred solution of 8.0 g. (0.035 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 125 ml. of 95% ethanol was added immediately a solution of 3.0 g. (0.046 mole) of sodium azide in 11 ml. of water. After the mixture was stirred for 1 hr., the precipitate was collected on a filter and washed with 75 ml. of 95% ethanol in portions, then with water; yield, 5.8 g., m.p. 123–128°. Recrystallization from 110 ml. of absolute ethanol gave 4.6 g. (56%) of white crystals, m.p. 131–133°; λ_{max}^{KBr} 4.59, 4.65μ (—N_3), 5.60μ (C_4=O of hydantoin), 5.75μ (C_2=O of hydantoin), 7.30, 8.57, 8.65μ (S → O of —SO_2N—).

Anal. Calcd. for $C_5H_7N_5O_4S$: C, 25.8; H, 3.02; N, 30.0; S, 13.8. Found: C, 26.2; H, 2.92; N, 29.8; S, 14.0.

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MENLO PARK, CALIF.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Bromination of Some 1,2,2-Triarylethylenes

N. P. BUU-HOÏ, ELIE LESCOT, JR., AND N. D. XUONG

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The synthesis of a number of new diversely substituted 1,2,2-triarylethylenes is described, and their bromination reactions are investigated. It is shown that in addition to normal substitution on the ethylene chain, nuclear bromination also can occur when reactive aryl or thienyl groups are present.

In the framework of a general investigation on potential chemical inhibitors of the secretions of the anterior pituitary,[1] 1,2,2-triarylethylenes were found to constitute an attractive group for the study of relationships between chemical structure and biological activity of this type.[2] The known fact that the introduction of further oxygen-containing radicals into the molecule of estradiol results in compounds with reduced estrogenic activity (*e.g.* estriol and 6-ketoestradiol) and which can act as antagonists of the mother-substance,[3] now suggested the study of 1,2,2-triarylethylenes derived from veratrole (those derived from anisole are known to be strong estrogens).[4]

1,2-Diphenyl-2-(3,4-dimethoxyphenyl)ethylene (I) was prepared by the reaction of benzylmagnesium chloride on 3,4-dimethoxybenzophenone and dehydration of the resulting tertiary carbinol by means of formic acid.[5] Bromination of this ethylene with one mole of bromine gave 1-bromo-1,2-diphenyl-2-(3,4-dimethoxyphenyl)ethylene (II); with two moles of bromine, nuclear bromination also occurred, the reaction product probably being 1-bromo-1,2-diphenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (III). This abnormal behavior is most likely due to the fact that in the molecule of the olefin (I), the position 6 in the veratryl radical is activated both by a *p*-methoxy group and by the *o*-styryl group; the influence of this latter group is in accord with the results of the theoretical computation of π-electron densities in the molecule of

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