reaction to subside between additions. The oxide was replaced by a globule of bright metallic mercury. When gas evolution became very slow an additional 2 g. of mercuric oxide was added and the mixture allowed to stand at room temperature for 2 hours with occasional shaking, dried (magnesium sulfate), filtered and evaporated at 35–40° (140 mm.). The clear oil (20 g.) deposited a crystalline solid on standing. Trituration with petroleum ether gave 9 g. (46.5%) of crude dibenzylmercury, m.p. 83–98°. Several crystallizations from nitromethane gave white needles, m.p. 110–113° (lit.[28] m.p. 111°).

Anal. Calcd. for $C_{14}H_{14}Hg$: C, 43.92; H, 3.68. Found: C, 43.91, H, 3.73.

The petroleum ether filtrate from the above trituration was evaporated at 70° (140 mm.) and the residue distilled. There was obtained 3.5 g. (23.6%) of 1-phenyl-2,2-dimethylpropane, b.p. 86–88° (20 mm.), shown by infrared analysis to be identical with an authentic sample [b.p. 75–76° (15 mm.)] prepared from benzylmagnesium chloride and *t*-butyl chloride [lit.[29] b.p. 185.6–186° (757.6 mm.)].

(28) P. Wolff, *Ber.*, **46**, 65 (1913).

(29) A. Bygden, *ibid.*, **45**, 3479 (1912).

Mercuric Oxide Oxidation of 1-*n*-Butyl-1-benzylhydrazine. (A) **In Methylene Dichloride.**—The reaction was carried out as indicated for the *t*-butyl derivative. Fractionation yielded 20% of a liquid, b.p. 90–94° (15 mm.), $n^{27}D$ 1.4870, shown by infrared analysis to be identical with an authentic sample of *n*-amylbenzene prepared from benzylmagnesium chloride and *n*-butyl *p*-toluenesulfonate by the method of Gilman and Beaber.[30]

(B) **In Ethanol.**—A stirred mixture of 25 g. of mercuric oxide[27] and 100 ml. of 95% ethyl alcohol was refluxed while 17.8 g. of the hydrazine was added in one portion. Within a short period a vigorous reaction set in and continued for 10–15 minutes after which the mixture was refluxed for 45 min. longer. The hot mixture was filtered and on standing overnight deposited 7 g. of white needles, m.p. 53–55°. Recrystallization of a portion from methanol gave the tetrazene XIII as small white crystals, m.p. 53.5–54.5°.

Anal. Calcd. for $C_{22}H_{32}N_4$: C, 74.95; H, 9.15. Found: C, 75.19; H, 9.23.

(30) H. Gilman and N. J. Beaber, THIS JOURNAL, **47**, 518 (1925).

AMHERST, MASS.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

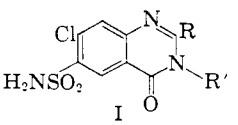
Quinazolinone Sulfonamides. A New Class of Diuretic Agents[1]

BY ELLIOTT COHEN, BETTY KLARBERG AND JAMES R. VAUGHAN, JR.

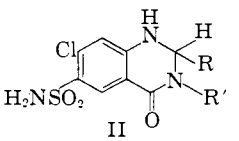
RECEIVED NOVEMBER 17, 1959

Investigation of diuretic activity in other heterocyclic systems has demonstrated that the benzothiadiazine 1,1-dioxide system is not unique in its effect on diuresis, natriuresis and chloruresis. A series of corresponding 7-chloro-6-sulfamyl-4(3H)-quinazolinones and 7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinones are described which have activity equal to or better than the benzothiadiazine 1,1-dioxides in experimental animals.

The current interest in orally active, heterocyclic diuretic agents, which are neither organic mercurial compounds nor primarily carbonic anhydrase inhibitors, has prompted intensive research in this field in many laboratories, both in this country and abroad.[2] In view of the well demonstrated clinical effectiveness of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide and its 3,4-dihydro derivative, much of this research has been directed toward compounds of this type or, to other, similar systems.[2b,3] In our laboratories, the approach has been somewhat different in that, as a first step, we sought to determine the necessity for and the importance of the ring sulfur–1,1-dioxide system on the diuretic, chloruretic and natriuretic activities reported for this class of compounds. Consequently we prepared a series of 7-chloro-6-sulfamyl-4(3H)-quinazolinones (I) and 7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinones (II) for evaluation.



I



II

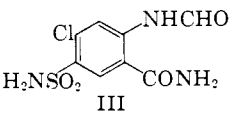
(1) A preliminary report on this work appears in THIS JOURNAL, **81**, 5508 (1959).

(2) (a) F. C. Novello and J. M. Sprague, *ibid.*, **79**, 2028 (1957); (b) Symposium on Chlorothiazide and its Derivatives, *Int. Rec. Med.*, **172**, Nos. 8, 9 (1959); see original articles for a very complete list of references.

(3) G. de Stevens, L. H. Werner, A. Halamandaris and S. Ricca, *Experientia*, **14**, 463 (1958).

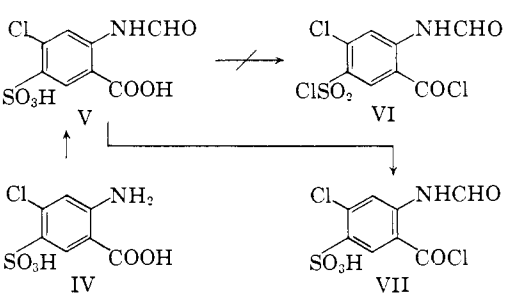
These examples, which may be considered as analogs of the benzothiadiazine-1,1-dioxides in which the cyclic $>SO_2$ group is replaced by $>C{=}O$, showed an activity equal to or better than that of the corresponding compounds in the benzothiadiazine series.[1]

Initial synthetic efforts in this program were directed toward the preparation of the diamide III. However, after sulfonation of 4-chloro-



III

anthranilic acid to give the sulfonic acid derivative IV, and subsequent formylation to V, all further attempts to make the diacid chloride VI, as an intermediate to the preparation of III, failed. The only product isolated was the mono-acid chloride VII.



V VI IV VII

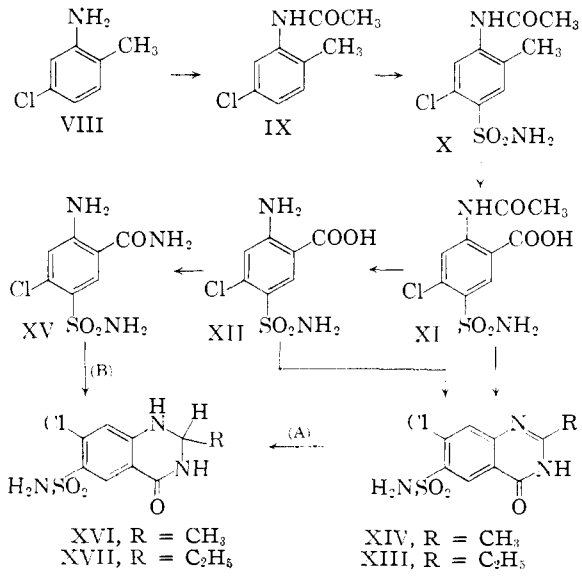
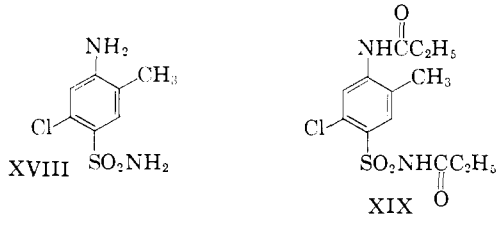


Fig. 1.

Our next approach, the one which was successfully carried out, is outlined in Fig. 1[4] for two representative quinazolinones (XVI and XVII).

Acetylation of 5-chlorotoluidine (VIII) formed the 5-chloro-*o*-acetotoluide (IX). Chlorosulfonation of this followed by treatment with aqueous ammonia gave 5-chloro-4-sulfamyl-*o*-acetotoluidide (X). Permanganate oxidation of X yielded the 4-chloro-5-sulfamyl-N-acetylanthranilic acid (XI). Deacetylation of XI with base or with acid formed 4-chloro-5-sulfamylanthranilic acid (XII). Cyclization of XII by fusion with propionanamide yielded 7-chloro-2-ethyl-6-sulfamyl-4(3H)-quinazolinone (XIII). In similar fashion, 7-chloro-2-methyl-6-sulfamyl-4(3H)-quinazolinone (XIV) was prepared by fusion of XI with urethan.[5]



For the preparation of the 1,2,3,4-tetrahydroquinazolinone derivatives, two synthetic routes were utilized. In the first of these (method A), the preformed quinazolinone was reduced directly using sodium borohydride in the presence of aluminum chloride in "diglyme" (diethylene glycol dimethyl ether) solution. In the second (method B), the intermediate N-acetylanthranilic acid (XI) was esterified and simultaneously deacetylated in methanol in the presence of sulfuric acid. Treatment of the resulting ester with concentrated ammonium hydroxide, without isolation, then resulted in the formation of the sulfamylbenzamide (XV).[6,7] Further treatment of this amide with diethylacetal or with propionaldehyde diethylacetal then yielded XVI and XVII, respectively.

The quinazolinones prepared are shown in Table I along with their analytical data and physical properties. The 1,2,3,4-tetrahydroquinazolinone derivatives are listed in Table II. In Table III is given a summary of the preliminary pharmacological evaluation of a few of these compounds in dogs.[8]

On oral administration in rats and dogs, a marked natriuresis and chloruresis, but at the same time only a relatively small increase in potassium excretion was observed.

In general, minor variations in R from H to lower alkyl had very little effect on the over-all activity but did effect the dose–response curves and the Na^+, Cl^- and K^+ excretion ratios. Substitution of R′ by alkyl, however, proved to be disadvantageous in that it reversed the Cl^- and K^+ excretion patterns in the few examples studied.

Conversion of the quinazolinones (I) to the 1,2,3,4-tetrahydroquinazolinones (II) resulted in an enhancement of oral diuretic activity on a dose/kg. basis in animals. It also reduced K^+ excretion as compared to Cl^- excretion (Table III).

Acknowledgment.—We wish to express our appreciation to Mr. L. Brancone and his staff for the microanalytical results and to Dr. J. R. Cummings and his staff for the pharmacological results reported.

Experimental[9]

4-Chloro-5-sulfoanthranilic Acid (IV).—A 17.2-g. (0.100 mole) sample of 4-chloroanthranilic acid was added to 15 ml. of ice-cold 30% oleum. To the resulting suspension 11.6 g. (0.100 mole) of chlorosulfonic acid was added dropwise. The mixture was heated at 95–100° for 2.75 hours and then the temperature was raised to 175–180° and maintained there for 2 hours. After cooling to room temperature, the dark oily material was poured onto 300 g. of cracked ice and stirred. The solid that formed was filtered off and air-dried overnight. The crude yield was 20.0 g. (79.5%).

A small sample was recrystallized from hot water to give slightly yellowish crystals, m.p. > 360° dec.

Anal. Calcd. for $C_7H_6NSO_5Cl$: C, 33.4; H, 2.39; S, 12.7; N, 5.57. Found: C, 33.3; H, 2.60; S, 12.5; N, 5.63.

4-Chloro-5-sulfo-N-formylanthranilic Acid (V).—A 20.0-g. (0.0800 mole) sample of 4-chloro-5-sulfoanthranilic acid was heated on the steam-bath for 2 hours with 200 ml. of 98% formic acid containing 20.0 g. of sodium formate. The solution was then evaporated to dryness and the resulting solid triturated with a small amount of ice-water. After standing in the refrigerator for 1 hour the solid was filtered off and air-dried overnight.

(4) Since our earlier communication[1] a U. S. Patent 2,910,488, by F. C. Novello has been issued in which the process and intermediates reported in Fig. 1 are disclosed. Also compound XX in Table I is described. Steps VIII through XII are essentially identical. Our results, therefore, are in accord with those reported by Dr. Novello.

(5) Another approach to the quinazolinones started with the chlorosulfonation of VIII to form 4-amino-6-chloro-*m*-toluenesulfonamide (XVIII) in high yield, but acetylation of XVIII gave a mixture of products instead of X. Using propionic anhydride, 4-chloro-5-sulfamyl-N,N′-dipropionylanthranilic acid (XIX) was obtained as the only crystalline product in 54% yield. Selective removal of the N^1-acyl group from this product, however, was not achieved.

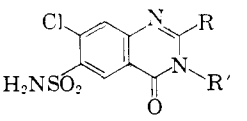
(6) S. M. Gadekar, to be published.

(7) In the course of this work, an alternate preparation of 2-amino-4-chloro-5-sulfamylbenzamide(XV) was devised. Treatment of 4-chloro-5-sulfamylanthranilic acid(XII) with ethyl chlorocarbonate and tri-*n*-butylamine in dimethylformamide at −10°, followed by ammonia yielded XV in 30% yield.

(8) We are indebted to Dr. J. R. Cummings and his associates of the Experimental Therapeutics Research Section, Pearl River Laboratories, for the pharmacological data reported.

(9) All melting points are uncorrected. Infrared spectra were taken as mineral oil mulls with a Perkin–Elmer Infracord. Ultraviolet spectra were taken in 0.1 *N* sodium hydroxide.

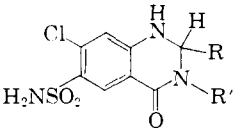
TABLE I



Compound	R	R′	Yield, %	M.p., °C.	Formula	Analyses, % Calculated C	H	N	S	Cl	Found C	H	N	S	Cl
XX	H	H	35	310–315	$C_8H_8N_3O_3SCl$	37.0	2.31	16.2	12.3	13.7	37.1	2.60	15.8	12.4	13.6
XIV	CH_3	H	52	>320	$C_9H_9N_3O_3SCl$	39.6	2.93	15.3	11.7	13.0	39.3	3.26	15.2	11.5	12.9
XXI	H	CH_3	46	238–240	$C_9H_9N_3O_3SCl$	37.0[a]	3.42	14.4	11.0	12.2	36.7	3.38	14.1	11.5	13.6
XXII	CH_3	CH_3	26	245	$C_{10}H_{10}N_3O_3SCl$	35.1[b]	4.57	12.3	9.38	..	35.1	4.06	12.3	9.37	..
XIII	C_2H_5	H	44	310–312	$C_{10}H_{10}N_3O_3SCl$	40.5[c]	3.71	14.1	10.8	12.0	40.9	3.98	13.7	10.7	13.0
XXIII	$(CH_3)_2CH$	H	20	>280	$C_{11}H_{12}N_3O_3SCl$	43.8	3.98	13.9	10.6	11.8	43.9	4.18	14.2	10.3	12.1
XXIV	OH	H	21	275	$C_8H_6N_3O_4SCl$	33.8[c]	2.45	14.9	11.2	..	33.7	2.89	15.4	11.4	..

[a] One mole of H_2O of crystallization. [b] Three moles of H_2O of crystallization. [c] One-half mole of H_2O of crystallization.

TABLE II



Compound	R	R′	Yield,[a] %	M.p., °C.	Formula	Analyses, % Calculated C	H	N	S	Cl	Found C	H	N	S	Cl
XXV	H	H	40	256–258	$C_8H_8N_3O_3SCl$	36.7	3.06	16.1	12.3	13.6	37.2	3.30	16.2	12.2	14.3
XVI	CH_3	H	60, 73[b]	285	$C_9H_{10}N_3O_3SCl$	39.2	3.63	15.3	11.7	12.9	39.1	3.60	15.1	11.8	12.7
XXVI	H	CH_3	25	257–259	$C_9H_{10}N_3O_3SCl$	39.2	3.63	15.3	11.7	12.9	39.1	3.76	15.4	11.5	12.9
XXVII	CH_3	CH_3	47	233–235	$C_{10}H_{12}N_3O_3SCl$	41.4	4.14	14.5	11.1	12.3	41.8	4.42	14.2	11.0	12.2
XVII	C_2H_5	H	28, 83[c]	248–250	$C_{10}H_{12}N_3O_3SCl$	41.4	4.14	14.5	11.1	12.3	41.0	4.52	14.3	11.1	12.4
XXVIII	$(CH_3)_2CH$	H	60	230	$C_{11}H_{14}N_3O_3SCl$	42.2	4.79	13.4	10.3	11.4	42.1	4.64	13.2	10.2	11.5
XXIX	n-C_4H_9	H	70[d]	219	$C_{12}H_{16}N_3O_3SCl \cdot {}^1/_4H_2O$	44.7	5.12	13.0	..	..	44.7	5.04	13.2	..	..

[a] All yields refer to hydride reductions of quinazolinones unless otherwise indicated. [b] This yield was obtained from XV with acetal in diglyme with hydrochloric acid. [c] This is described in the Experimental; propionaldehyde instead of its acetal has also been used. [d] This yield was obtained from XV with valeraldehyde in diglyme or ethanol with hydrochloric acid.

TABLE III

AVERAGE PERCENTAGE CHANGE FROM CONTROL IN ELECTROLYTE EXCRETION. ORAL ADMINISTRATION IN DOGS

	Dose, mg./kg.	Cl^- (24 hr.)	K^+ (24 hr.)	Cl^-/K^+ (24 hr.)
Unreduced compounds				
Chlorothiazide	20	266	112	2.38
XX	20	261	98	2.66
XIV	20	223	76	2.94
Reduced compounds				
Dihydrochlorothiazide	1	201	57	3.52
Dihydrochlorothiazide	5	374	122	3.10
XXV	1	150	9	16.7
XXV	5	360	58	6.21
XVI	1	49	22	2.23
XVI	5	212	24	8.83
XVII	1	215	101	2.12
XVII	5	291	32	9.10

The yield of N-formyl material was 11.4 g. (52%). The product had bands in the carbonyl region of the infrared spectrum at 5.83 and 5.95 μ corresponding to the N-formyl and carboxylic acid absorptions, respectively.

A small amount was recrystallized from dioxane and water; m.p. >360°.

Anal. Calcd. for $C_8H_5NSO_6NaCl.H_2O$: C, 30.7; H, 2.19; N, 4.34; S, 10.0. Found: C, 30.7; H, 1.88; N, 4.35; S, 9.57.

Attempts to Form the Diamide III. Formation of the 2-N-Formamido-4-chloro-5-sulfobenzoyl Chloride (VII).—A 1.0-g. sample of V was heated with a mixture of 10 ml. of $POCl_3$ and 1.5 g. of PCl_5 for 5 hours on the steam-bath. The mixture was cooled and poured onto ice to give a yellow crystalline material. The infrared spectrum showed the presence of an acid chloride at 5.60 μ and the acid band at 5.95 μ had disappeared.

Anal. Calcd. for carboxyl chloride $C_8H_5NSO_5Cl_2 \cdot H_2O$: C, 30.4; H, 2.21; N, 4.44; S, 10.1; Cl, 22.50. Found: C, 29.6; H, 2.06; N, 4.71; S, 9.49; Cl, 22.95.

Subsequent reactions using PCl_5 alone at 170° for 3 hours, $POCl_3$ alone or $SOCl_2$–pyridine with either the starting material or the monoacid chloride followed by ammonia did not give any crystalline material.

5-Chloro-4-sulfamyl-*o*-acetotoluidide (X).—A mixture of 58 g. (0.32 mole) of 5-chloro-*o*-acetotoluidide (IX)[10] and 100 ml. of ice-cold chlorosulfonic acid containing 17 g. of sodium chloride was heated on the steam-bath for 2 hours. After cooling, the solution was poured onto 500 g. of ice and stirred. The crude "sulfonyl chloride" was filtered off and air-dried.

The partially damp cake was added to 500 ml. of concentrated ammonium hydroxide, stirred and warmed for 0.5 hour while the starting material dissolved and the product precipitated out. After standing for an additional 0.5 hour, the mixture was filtered and a pale white crystalline material was obtained. A sodium hydroxide solution of the solid was clarified with activated carbon and acidified with concentrated hydrochloric acid. After cooling the solution, 40 g. of product (51% based on recovered "sulfonyl chloride") was filtered off, m.p. >265°. The infrared spectrum showed the characteristic bands for a sulfonamide group at 7.6 and 8.6 μ.

Anal. Calcd. for $C_9H_{11}N_2O_3SCl$: C, 41.1; H, 4.20; N, 10.6; S, 12.2; Cl, 13.5. Found: C, 41.0; H, 4.31; N, 10.6; S, 11.9; Cl, 13.8.

There was also obtained 6.0 g. of crystals which were insoluble in 1.0 *N* sodium hydroxide. They gave a positive silver nitrate test and an infrared spectrum which was very similar to that of the "sulfonyl chloride" obtained in the first step.

By concentrating the ammoniacal filtrate from the initial precipitate, a third crop (13 g.) of crystals was obtained. From the infrared spectrum and the fact that ammonia

(10) R. E. Lutz, G. Ashburn, J. A. Freek, R. J. Jordan, N. H. Leake, T. A. Martin, R. A. Rowlett, Jr., and J. W. Wilson, THIS JOURNAL, **68**, 1285 (1946).

is evolved when the crystals are refluxed in aqueous base, this is apparently the ammonium salt of the sulfonic acid.

4-Chloro-5-sulfamyl-N-acetylanthranilic Acid (XI).—A 40-g. (0.15 mole) sample of the sulfonamide X was added batchwise to 50 g. (0.32 mole) of potassium permanganate dissolved in 500 ml. of warm water. The mixture was stirred while heating on the steam-bath for 90 minutes. After cooling the mixture, the precipitated manganese oxide was filtered off, washed with 50 ml. of dilute base, and the combined filtrates were clarified with activated carbon and then acidified. After cooling the resulting mixture overnight, 14 g. (37%) of product was obtained. An infrared spectrum of this solid showed bands in the carbonyl region at 5.85 and 6.0 μ. This material is soluble in bicarbonate as contrasted to the starting material which required sodium hydroxide. The compound (XI), without purification, was used in the next reaction.

A small sample was dissolved in 1 *N* sodium hydroxide, clarified with activated carbon and acidified with concentrated hydrochloric acid to yield white crystals, m.p. 254–256°.

Anal. Calcd. for $C_9H_9N_2O_5SCl$: C, 36.9; H, 3.08; N, 9.57; S, 11.0; Cl, 12.1. Found: C, 37.3; H, 3.60; N, 9.92; S, 10.7; Cl, 12.3.

4-Chloro-5-sulfamylanthranilic Acid (XII).—A 10-g. (0.034 mole) sample of the N-acyl compound XI was dissolved in a mixture of 200 ml. of ethanol and 200 ml. of hydrochloric acid while warming and stirring. The solution was refluxed for 5.5 hours on the steam-bath, cooled, and then evaporated *in vacuo* almost to dryness. To the residue was added 20 ml. of 1.0 *N* sodium hydroxide and after clarifying with activated carbon, the solution was acidified to congo red and cooled overnight.

White crystalline material was obtained; 5.5 g. (65%), m.p. 230–235°. An analytical sample, m.p. 275°, was formed by dissolving the solid in base and reprecipitating with acid.

Anal. Calcd. for $C_7H_7N_2O_4SCl$: C, 33.5; H, 2.79; N, 11.2; S, 12.8; Cl, 14.2. Found: C, 33.3; H, 2.85; N, 11.2, 12.6; Cl, 14.1.

Yields in the range of 90% have been realized in subsequent saponifications with 3 *N* sodium hydroxide.

7-Chloro-2-ethyl-6-sulfamyl-4(3H)-quinazolinone (XIII).—A mixture of 2 g. (0.008 mole) of 4-chloro-5-sulfamylanthranilic acid (XII) and 2 g. (0.03 mole) of propionamide was heated at 185–190° for 4 hours. The product was cooled and stirred with 10% sodium bicarbonate for an hour to remove the starting material. The remaining crystals were filtered off and dissolved in 20 ml. of 1 *N* sodium hydroxide. After clarifying the basic solution with activated carbon, concentrated hydrochloric acid precipitated 1 g. (44%) of product. A 0.1-g. sample was recrystallized from base and acid for analysis; m.p. >250°; in the infrared bands at 5.93, 6.23 μ; in the ultraviolet, λ_{max} 295 mμ, ϵ 31,200.

7-Chloro-6-sulfamyl-2-methyl-4(3H)-quinazolinone (XIV).—A 1.0-g. (0.0034 mole) sample of *N*-acetyl-4-chloro-5-sulfamylanthranilic acid (XI) and 1.0 g. (0.011 mole) of urethan were mixed and heated at 180–190° for 3 hours. The progress of the reaction was followed by measuring the CO_2 emitted. When CO_2 was no longer evolved, the reaction flask was cooled and 10 ml. of 10% sodium bicarbonate was added. The mixture was stirred for an hour to solubilize any unreacted acid and filtered. The crude product was dissolved in 5 ml. of 1 *N* sodium hydroxide, extracted first with ethyl acetate, then ethyl ether, and the aqueous layer containing the product was treated with activated carbon and filtered. The purified white product was obtained by acidification with concentrated hydrochloric acid; in the infrared, bands at 5.92, 6.21 μ; in the ultraviolet, λ_{max} 293 mμ, ϵ 42,800.

2-Amino-4-chloro-5-sulfamylbenzamide (XV). A.—Equimolar amounts of the anthranilic acid XII, tri-*n*-butyl(or triethyl)-amine and ethyl chlorocarbonate were stirred in dimethylformamide for 5–10 minutes at −5 to −10°. Excess ammonia (aqueous or liquid) was added and the mixture was stirred in the cold for 10–30 minutes, and then on the steam-bath for 10–30 minutes. After concentrating the solution to dryness, water was added and the solid filtered off. Stirring with bicarbonate removed the starting material (50–70%), and the remaining solid was recrystallized from ethanol–water. The yields ranged from 20–30%, m.p. 282–284° dec.; reported[4] 277–278° dec.

Any increase in temperature caused the formation of a ureido acid.[11] An excess of reagents, lower temperature, longer reaction time at −10° or omission of the tertiary amine caused lower yields of the amide and recovery of starting material. Using diglyme or tetrahydrofuran as solvents does not increase the yield.

B.—The amide can also be obtained directly from the N-acetyl acid XI by forming the glycol or methyl ester and amidating either with or without isolating the initially formed ester.[6]

General Method of Preparation of the Dihydroquinazolinones in Table II by Benzamide Aldehyde Cyclizations. 7-Chloro-2-ethyl-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinone (XVII).—A 1.0-g. (0.0040 mole) sample of 2-amino-4-chloro-5-sulfamylbenzamide was refluxed in 100 ml. of ethanol with two drops of concentrated hydrochloric acid and 0.70 ml. (0.0044 mole) of propionaldehyde diethylacetal for one hour. The solution was then evaporated to dryness *in vacuo*, and the residue triturated with 25 ml. of water to give 0.90 g. (75%) of white crystals, m.p. 243–245°. Recrystallization from acetone–water afforded 0.75 g. of the desired product, m.p. 250–252°. The infrared and ultraviolet spectra were identical with that of XVII prepared by hydride reduction. There was no depression in the melting point when the samples were mixed.

4-Amino-6-chloro-*m*-toluenesulfonamide (XVIII).—A mixture of 0.30 g. (0.0051 mole) of sodium chloride and 3.0 ml. (0.046 mole) of cold chlorosulfonic acid was kept in an ice-bath while 1.0 g. (0.0071 mole) of 5-chlorotoluidine was added dropwise. The reaction mixture was heated to 145° and maintained there for 2 hours. The solution was cooled, poured onto ice, and an off-white precipitate was filtered off and washed with ice-water.

The partially dried solid was added to anhydrous liquid ammonia and the solution allowed to evaporate at room temperature. The product, 1.2 g. (75%), was dissolved in 1.0 *N* sodium hydroxide, clarified with activated carbon, acidified with hydrochloric acid and filtered off. For further purification, the solid was recrystallized from ethanol–water; m.p. 242–244°.

Anal. Calcd. for $C_7H_9N_2SO_2Cl$: C, 38.0; H, 4.07; N, 12.7; S, 14.5; Cl, 16.1. Found: C, 38.2; H, 4.40; N, 12.9; S, 14.7; Cl, 16.5.

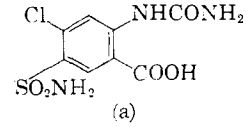
4-Chloro-5-sulfamyl-N,N′-(dipropionyl)-anthranilic Acid (XIX).—A 1.0-g. (0.0040 mole) sample of 4-chloro-5-sulfamylanthranilic acid (XII) was heated on a steam-bath with 50 ml. of propionic anhydride for 3 hr. The resulting solution was poured into 200 cc. of ice-water, forming two layers. Stirring caused the layers to merge and a solid to precipitate. The solid was filtered off and washed with cold water to yield 0.65 g. (54%) of white solid, m.p. 237–238° (efferv.). The melting point was unchanged after redissolving a sample in bicarbonate and reprecipitating with acid.

Anal. Calcd. for $C_{13}H_{15}N_2SClO_6 \cdot {}^1/_2H_2O$: C, 42.0; H, 4.31; N, 7.57; S, 8.54; Cl, 9.59. Found: C, 41.9; H, 4.52; N, 7.67; S, 8.46; Cl, 9.99.

7-Chloro-6-sulfamyl-4(3H)-quinazolinone (XX).—A 5.0-g. (0.020 mole) sample of XII was heated with 5 ml. of formamide at 170–175° for 3.5 hours. The resulting light brown mixture was cooled and poured into 25 ml. of cold water to form crystals and some oil. When the oil was triturated with methanol and fresh water added, more crystals formed. After filtering off the crystals, 1.8 g. (35%) of product resulted.

A 0.10-g. sample was dissolved in 0.1 *N* sodium hydroxide, clarified with activated carbon and acidified with hydrochloric acid to yield slightly off-white crystals. This process was repeated and faint tan-colored crystals, m.p. 310–315°, resulted; in the infrared, bands at 5.87 and 6.22 μ; in the ultraviolet λ_{max} 295, ϵ 44,000.

(11) This compound, m.p. 218°, appears to be (a) from its bicarbonate solubility, infrared spectrum and probable mode of formation.



(a)

7-Chloro-3-methyl-6-sulfamyl-4(3H)-quinazolinone (XXI).—A 1.0-g. sample (0.0040 mole) of 4-chloro-5-sulfamylanthranilic acid (XII) was heated at 175–180° with 1.0 ml. of N-methylformamide for 4 hours. The reaction product was cooled, triturated with 5 ml. of methanol, and the resultant off-white crystals were filtered off. The solid was stirred with 5 ml. of 10% sodium bicarbonate to remove traces of starting material and again filtered off. The solid was then dissolved in 5 ml. of 1.0 *N* sodium hydroxide, clarified with activated carbon and precipitated with hydrochloric acid; yield 0.25 g. On a second run the yield was doubled; in the infrared, bands at 6.00, 6.23 μ; in the ultraviolet λ_{max} 282 mμ, ϵ 32,800.

7-Chloro-2,3-dimethyl-6-sulfamyl-4(3H)-quinazolinone (XXII).—A 0.5-g. (0.002 mole) sample of 4-chloro-5-sulfamylanthranilic acid (XII) and 0.5 ml. of N-methylacetamide were heated together at 195–200° for 4 hours. After cooling, the residue was triturated with methanol and 5 ml. of water was added. An oil formed which crystallized in the refrigerator overnight. The solid (0.50 g.) was stirred with 10% sodium bicarbonate and then filtered off to yield 0.15 g. (26%) of light yellow crystals. For further purification, the sample was dissolved in 5 ml. of 1 *N* sodium hydroxide, clarified with activated carbon and precipitated by the addition of hydrochloric acid; m.p. 245°.

7-Chloro-2-isopropyl-6-sulfamyl-4(3H)-quinazolinone (XXIII).—A mixture of 2.5 g. (0.010 mole) of 4-chloro-5-sulfamylanthranilic acid (XII) and 2.5 g. (0.029 mole) of isobutyramide was heated at 190° for 3.5 hours in an open flask. The residue was taken up in hot methanol, concentrated slightly and water was added. A tan solid (1.0 g.) formed and was filtered off. The solid was stirred with bicarbonate to remove starting material and after filtering off again, the solid was taken up in 1.0 *N* sodium hydroxide, clarified with activated carbon and acidified with concentrated hydrochloric acid. The product was then recrystallized from acetone–water to yield 0.20 g. (6.8%) of material, m.p. 280°. A second recrystallization from ethanol yielded white needles, m.p. 290°; in the infrared, bands at 6.01, 6.24 μ; in the ultraviolet, λ_{max} 295 mμ, ϵ 34,400.

7-Chloro-2,4-dihydroxy-6-sulfamylquinazoline (XXIV).—A 0.50-g. (0.0020 mole) sample of 4-chloro-4-sulfamylanthranilic acid (XII) was heated with 0.50 g. (0.0083 mole) of urea at 180° for 3 hours. Ammonia was evolved during this time. Sodium bicarbonate solution (10%) was added to the cooled residue and the mixture was stirred to dissolve unreacted starting material. The remaining crystals (0.30 g.) were filtered off and then recrystallized by dissolving in 5 ml. of 1 *N* sodium hydroxide, clarifying with activated carbon and acidifying with 6 *N* hydrochloric acid; yield 0.15 g. (21%), m.p. 275°. The infrared spectrum showed carbonyl absorptions at 5.75 and 5.85 μ; in the ultraviolet, λ_{max} 264 mμ, ϵ 55,000; λ_{max} 325 mμ, ϵ 15,600.

Urethan can be substituted for urea with the same results.

General Method for the Preparation of the Tetrahydroquinazolinones (Table II) by Hydride Reduction. 7-Chloro-6-sulfamyl-1,2,3,4-tetrahydro-4(3H)-quinazolinone (XXV).—Aluminum chloride (1.03 g., 0.0077 mole) was added to 250 ml. of dry diglyme in an ice-bath. The stirred mixture was then warmed while 2.0 g. (0.0077 mole) of 7-chloro-6-sulfamyl-4(3H)-quinazolinone was added. A solution of 1.4 g. (0.037 mole) of sodium borohydride in 70 ml. of dry diglyme was added dropwise. The orange mixture was kept at 85° for one hour. The flask was cooled in ice and 40 ml. of water was slowly added. Dilute hydrochloric acid was added to obtain a strongly acidic, clear solution which was then concentrated *in vacuo* to dryness. The solid residue was triturated with cold water to yield 0.90 g. of solid melting over a broad range. Recrystallization from 50% aqueous acetone gave 0.65 g. (33%) of pale yellow crystals, m.p. 254–256°.

A 0.20-g. sample was recrystallized in the same manner to yield 0.15 g. of needle crystals, m.p. 256–258°; in the infrared, bands at 6.01, 6.24 μ (a hypsochromic shift of 0.14 μ from the unreduced compound); in the ultraviolet λ_{max} 265 mμ, ϵ 32,000.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Action of Grignard Reagents. XVIII. Action of Organomagnesium Compounds on 4-Methyl-2,3-benzoxaz-1-one and on Phthalazones

BY AHMED MUSTAFA, ABDEL HAMID HARHASH AND ABDEL ALLIM SHOEB SALEH

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Treatment of 4-methyl-2,3-benzoxaz-1-one (Id) with Grignard reagents brought about cleavage of the hetero ring with the formation of IId–g. Addition of phenylmagnesium bromide to phthalazone (IIIa), 1-phenylphthalazone (IIIb), 1-phenylthiophthalazone (Xa) or its isomer IXa, and 1-phenyl-3-acetylphthalazone (IIIc), followed by hydrolysis, effects the formation of 1,4-diphenylphthalazine (IV) together with diphenylmethylcarbinol in the case of IIIc. Compound IV now has been obtained either by the action of phenylmagnesium bromide on 1-phenyl-4-chlorophthalazine, which exhibits the reactivity characteristic of chloro heterocyclic compounds containing the group —N=CCl— or 1,4-dichlorophthalazine.

Phthalazine undergoes 1,2-addition of phenylmagnesium bromide to the C=N, accompanied by autoxidation, to give 1-phenylphthalazine. Treatment of 1,3-diphenylphthalazone (IIIe) with phenyl-, *p*-tolyl-, benzyl- and methylmagnesium halides result in the formation of reaction products, believed to have structures like Va-b and VIa-b, respectively. Similar reaction has been also observed when 1-methyl-3-phenylphthalazone (IIIf) is treated with benzylmagnesium chloride, yielding VIc. The 4-mercaptophthalazine derivatives IXa-c or the corresponding 4-thiophthalazone derivatives Xa–c, as well as the 4-thiophthalazone derivatives XIa–c are obtained by the action of phosphorus pentasulfide on the corresponding phthalazone derivative.

Recently, Mustafa and co-workers[1] have shown that treatment with phenylmagnesium bromide brought about opening of the oxazone ring in the 2,3-benzoxaz-1-ones Ia–c; which yielded the corresponding oximes of 2-formyl- (IIa), 2-benzoyl- (IIb) and 2-(α-naphthoyl)-triphenylcarbinol (IIc), respectively.

We now have extended the study of this reaction and investigated the action of organomagnesium compounds on 4-methyl-2,3-benzoxaz-1-one (Id). Thus, treatment with phenylmagnesium bromide brought about opening of the oxazone ring in Id, which yielded the corresponding oxime of 2-acetyltriphenylcarbinol (IIe). Similarly, the corresponding oximes of 2-acetyldimethylphenylcarbinol (IId), 2-acetyl-di-*p*-tolylphenylcarbinol (IIf) and 2-acetyldibenzylphenylcarbinol (IIg) are obtained by the action of methyl-, *p*-tolyl- and benzylmagnesium halides on Id, respectively. The reactions of phthalazones (III), in general, parallel to a great extent

(1) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby and A. E. A. Hassan, THIS JOURNAL, **77**, 1612 (1955).