hemolyticus, group C (Pion strain B.W., C.N.4.). Thus both the mouse toxicity of the compound and its effect upon the course of infection could be studied simultaneously. Compounds were suspended in 5% gum acacia and given in a dose of 0.5 ml. immediately after intraperitoneal infection with 0.2 ml. of a 10^{-3} dilution of 6-hr. blood broth culture of the streptococcus.

B. Evaluation of Compounds against *Candida albicans* Infection in Mice. (i)—A technique described by Lindh,[29] in which an infection of the gastrointestinal tract of mice was produced by administering a diluted fluid Sabouraud medium culture of *C. albicans* in lieu of drinking water. The compound under investigation was administered, at previously determined nontoxic doses in the food, and quantitative estimations of *C. albicans* were made from fecal pellets. Only active compounds, such as the control drug nystatin, which are not appreciably absorbed from the gastrointestinal tract, effectively suppressed this infection. Compounds potentially suitable for topical application may be revealed by this method.

(ii)—To study activity against systemic *C. albicans* infection, mice were injected intravenously with a culture of *C. albicans* of standard density and dosed subcutaneously with 50 mg./kg. of the compound under investigation, the initial dose being given 2 hr. after infection and subsequent doses 24 and 48 hr. later. Unprotected mice usually died within 21 days due to systemic spread of infection from primary kidney lesions. Amphotericin in 3 doses of 12.5 mg./kg. protected the majority of mice. Details of this technique were kindly supplied by Mr. L. J. Hale, Boots Pure Drug Co. Ltd., Nottingham, England.

C. Activity against *Trichomonas vaginalis* Infection in Mice.—The literature describing attempts to induce trichomonas infection in laboratory animals and the experimental chemotherapy of such infection has been comprehensively reviewed by Ryley and Stacey.[30] The following technique was selected because in infection caused by *T. vaginalis*, topically active drugs have been largely superseded by those that are active after oral administration.

Mice, in groups of 10, were injected subcutaneously with approximately 2×10^6 *T. vaginalis* in 0.5 ml. of liver-infusion medium and immediately given a single oral dose of 100 mg./kg. of compound; similar doses were given on each of the following 4 days. The mice were killed 7 days after infection and examined for trichomonal subcutaneous lesions. The majority of mice given doses of metronidazole (12.5 mg./kg.) on this schedule were free from lesions.

Acknowledgments.—The authors thank Miss J. Mallion and Miss P. Dougherty for the microanalyses, and Mrs. M. Way, Miss M. Wall, and Mr. B. Bashford for skilled technical assistance.

(29) H. F. Lindh, *Antibiot. Chemotherapy*, **9**, 226 (1959).

(30) J. F. Ryley and G. J. Stacey, *Parasitology*, **53**, 303 (1963).

New Sulfonamides

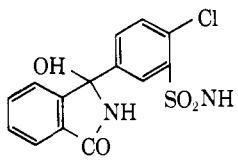
J. M. LOYNES, H. F. RIDLEY, AND R. G. W. SPICKETT

Smith Kline and French Laboratories Ltd., Welwyn Garden City, Hertfordshire, England

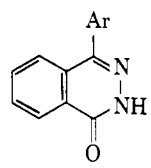
Received March 9, 1965

The preparation is described of several 4-aryl-1(2H)-phthalazinones and 3-aryl-3,4-dihydro-(2H)-1,2,4-benzothiadiazine 1,1-dioxides. The compounds were inactive in diuretic tests.

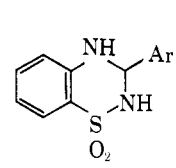
The isoindoline derivative I (chlorthalidone),[1] although developed from the disulfonamide carbonic anhydrase inhibitors, was shown to have a similar electrolytic excretion pattern to the thiazides.[2,3] It differs structurally from the thiazides in that the heterocycle is attached to the benzene ring bearing the sulfonamido and halogen groups by a single bond to a quaternary carbon atom and is thus, unlike the thiazides, nonplanar. In order to find whether other acidic heterocyclic ring structures could replace the isoindoline ring of I, the compounds II and III (Ar = 4′-Cl-3′-$H_2NSO_2C_6H_3$) and related structures were prepared for testing as diuretics (see Tables I and II).



I



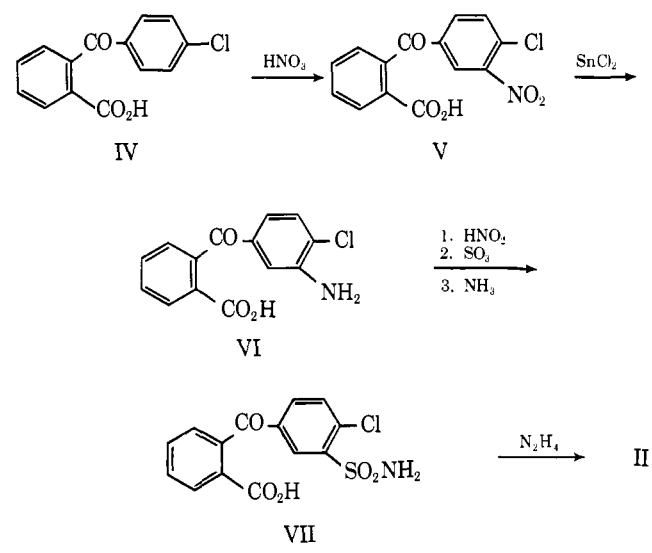
II



III

The phthalazinone II was prepared from 4′-chlorobenzophenone-2-carboxylic acid by the route shown in Chart I.

CHART I



4′-Chloro-3′-nitrobenzophenone-2-carboxylic acid (V) was first obtained[4,5] by nitration of 4′-chlorobenzophenone-2-carboxylic acid (IV) in a sulfuric–nitric acid mixture. In our hands this procedure led to a mixture of dinitro compounds. Nitration of IV with fuming nitric acid at 90° gave a mixture of mono and dinitro compounds,

(1) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(2) E. G. Stenger, H. Wirz, and R. Pulver, *Schweiz. Med. Wochschr.*, **89**, 1126, 1130 (1959).

(3) R. Veyrat, E. F. Arnold, and A. Duckert, *ibid.*, **89**, 1133 (1959).

(4) Basler Chem. Fabrik., German Patent 148,110 (1903); *Chem. Zentr.*, I, 328 (1904).

(5) W. Bradley and H. E. Nurster, *J. Chem. Soc.*, 2180 (1951).

but at room temperature the required mononitro compound (V) was obtained in 80% yield. Nitration did not occur with nitric acid in acetic acid.

Reduction of the nitro acid (V) with stannous chloride gave the amino acid (VI) in 57% yield. Other methods of chemical reduction,[6,7] and catalytic hydrogenation, gave lower yields of the amino acid.

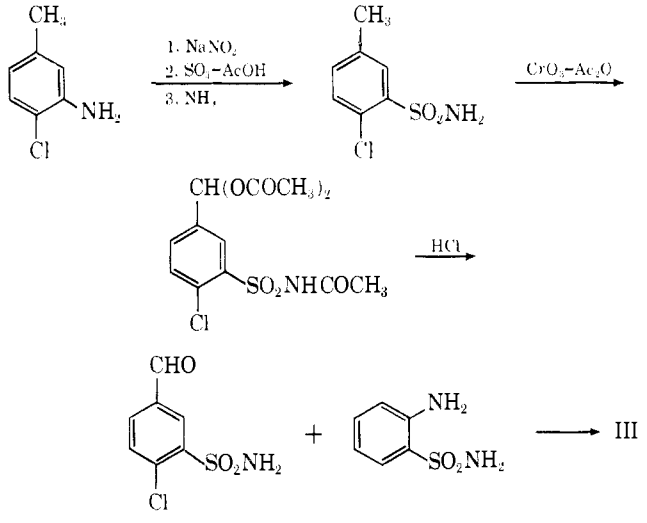
The amino acid (VI) was converted to the sulfonyl chloride and then to the sulfonamide (VII) by Stoll's method.[1] Reaction with hydrazine gave the required phthalazinone II. Condensation of the acid V with hydrazine gave 4-(4-chloro-3-nitrophenyl)-1(2H)-phthalazinone.

Several 2-substituted 4-phenyl-1(2H)-phthalazinones were also prepared for testing. 2-Benzyl-, 2-(2-dimethylaminoethyl)-, and 2-[3-(4-methylpiperazinyl)-propyl]-4-phenyl-1(2H)-phthalazinone were prepared by alkylating 4-phenyl-1(2H)-phthalazinone in alcohol in the presence of base. 4-Phenyl-2-(2-hydroxyethyl)-1(2H)-phthalazinone was obtained by condensation of benzophenone-2-carboxylic acid with hydroxyethylhydrazine, and on treatment with thionyl chloride gave 4-phenyl-2-(2-chloroethyl)-1(2H)-phthalazinone. When the latter compound was heated at 100° for 2 days with dimethylamine in ethanol, 30% of the starting material was recovered. 2-(2-Dimethylaminoethyl)-4-phenyl-1(2H)-phthalazinone could not be isolated from the tarry residues.

The substituted dihydrobenzothiadiazine dioxide (III, Ar = 4′-Cl-3′-$H_2NSO_2C_6H_3$) was prepared by condensing *o*-aminobenzenesulfonamide with 2-chloro-5-formylbenzenesulfonamide.

2-Chloro-5-formylbenzenesulfonamide (IX) was prepared from 6-chloro-*m*-toluidine as shown in Chart II.

CHART II



6-Chloro-*m*-toluidine was converted (60% over-all yield) to 6-chloro-*m*-toluenesulfonamide by Stoll's method.[2] Oxidation of this compound with chromium trioxide in acetic anhydride gave a triacetyl compound in 67% yield. Elemental analysis and infrared spectral data confirmed the structure as VIII. Acetylation of the sulfonamido group under similar conditions has been described by Topliss.[8] In the infrared spectrum of VIII, bands at 1762 and 1722 cm.$^{-1}$ were attributed to C=O vibrations due to the O-acetyl groups and N-acetylsulfamyl group, respectively. A band at 1725 cm.$^{-1}$ has been found by Topliss to be associated with the N-acetylsulfamyl group in 2-acetylsulfamylacetanilide. Hydrolysis of the triacetate gave the free aldehyde (IX) which was characterized as its dinitrophenylhydrazone.

Several other 3-aryldihydrobenzothiadiazine 1,1-dioxides (III) were prepared by condensing the appropriate aldehyde with *o*-aminobenzenesulfonamide.[9]

None of the compounds possessed diuretic activity when tested in the saline- or water-loaded rat.

Experimental[10]

Nitration of 4′-Chlorobenzophenone-2-carboxylic Acid. A.—4′-Chlorobenzophenone-2-carboxylic acid (IV) (29.96 g., 0.1 mole) was added slowly with stirring to a mixture of concentrated H_2SO_4 (55 ml.) and concentrated HNO_3 (45 ml.), keeping the temperature below 30°. After the addition was complete, the mixture was heated at 80° for 1 hr. and poured onto ice. The solid was collected and recrystallized from 2-propanol, m.p. 187–189°. Thin layer chromatography on silica in methanol–hexane (3:2) showed the product to be a mixture (R_f 0.18 and 0.49). Elemental analysis corresponded to a mixture of dinitro compounds.

Anal. Calcd. for $C_{14}H_7ClN_2O_7$: C, 47.9; H, 2.01; Cl, 10.1; N, 8.0; equiv. wt., 351. Found: C, 47.5; H, 1.94; Cl, 10.4; N, 7.7; equiv. wt., 353.

Analytical reduction[11] with titanous chloride confirmed the presence of two nitro groups.

B.—A mixture of IV (10 g.) and fuming HNO_3 was evaporated to dryness on a steam bath. The residue was washed with water and recrystallized to constant melting point from 2-propanol, m.p. 203–205° (lit.[4] m.p. 202–204°), yield 5.4 g. (45%).

Anal. Calcd. for $C_{14}H_8ClNO_5$: Cl, 11.6; equiv. wt., 306. Found: Cl, 11.5; equiv. wt., 306.

Quantitative reduction with $TiCl_3$ confirmed the presence of one nitro group.

From the mother liquors the dinitro mixture was obtained. When this experiment was repeated with 100 g. of IV a mixture of mono and dinitro compounds was isolated, m.p. 201–203°. When IV was allowed to stand in fuming nitric acid overnight only a mixture of dinitro compounds could be isolated.

C.—IV (10 g.) was added with stirring to fuming HNO_3 (40 ml.) the temperature being kept below 25°. After being stirred for 5 min., the mixture was poured onto ice and worked up in the usual manner to give 9.0 g. (80%) of the mononitro acid, m.p. 204–205°. A 78% yield was obtained when the experiment was repeated with 100 g. of IV.

3′-Amino-4′-chlorobenzophenone-2-carboxylic Acid.—To a stirred, cooled (below 25°) solution of 4′-chloro-3′-nitrobenzophenone-2-carboxylic acid (10 g., 0.033 mole) in ethanol (100 ml.) was added a solution of $SnCl_2$ (22.6 g., 0.1 mole) in concentrated HCl (20 ml.). After the addition was complete, the mixture was stirred at 40° for 45 min. The solvent was then evaporated *in vacuo*, and the residue was brought to pH 5 with dilute Na_2CO_3 and extracted several times with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to give a bright yellow solid. Crystallization from benzene gave pale yellow needles of the amino acid (5.2 g., 57%), m.p. 179–180° (lit.[5] m.p. 181.5–182°).

Phthalazinones. Method A. 4-(4-Chloro-3-sulfamyl)phenyl-1(2H)-phthalazinone.—A mixture of 4′-chloro-3′-sulfamylbenzo-

(6) H. W. Hereward, L. J. Hooley, and J. Thomas (to Scottish Dyes Ltd.), British Patent 311,465 (1928); *Chem. Abstr.*, **24**, 972 (1930).

(7) M. Hido, S. Kato, and M. Maezawa, *Kogyo Kagaku Zasshi*, **61**, 1268 (1958).

(8) J. G. Topliss, *J. Org. Chem.*, **27**, 654 (1962).

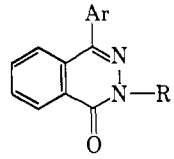
(9) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. De Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

(10) Melting points were recorded using an electrothermal melting point apparatus comprising a gas-heated block and thermometer calibrated for exposed stem. Microanalyses are by Mr. M. Graham and infrared spectra by Miss E. V. Eggintod (Analytical Laboratories, Smith Kline and French Laboratories Ltd.).

(11) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 128.

TABLE I

2-ALKYL-4-ARYL-1(2H)-PHTHALAZINONES

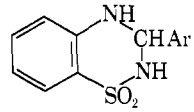


Ar	R	Method	Crystn. solvent	M.p., °C.	Formula	—C, %— Calcd.	Found	—H, %— Calcd.	Found	—N, %— Calcd.	Found
4'-Cl-3'-$H_2NO_2SC_6H_3$	H	A	Aq. DMF[a]	323–325	$C_{14}H_{10}ClN_3O_3S$	49.5	50.1	2.98	3.0	12.7	12.5
4'-Cl-3'-$NO_2C_6H_3$	H	A	Aq. ethanol	277–278	$C_{14}H_8ClN_3O_3$	56.1	56.1	2.63	2.63	13.9	14.0
C_6H_5	$CH_2C_6H_5$	B[b,c]	DMF–ethanol (1:1)	186–187	$C_{21}H_{16}N_2O$	80.7	81.0	5.16	5.16	9.07	9.3
C_6H_5	$CH_2CH_2N(CH_3)_2$	B	Petr. ether	101–103.5	$C_{18}H_{19}N_3O$	73.7	73.6	6.53	6.60	14.3	14.3
C_6H_5	$(CH_2)_3N$ NCH_3	B	Petr. ether	117–119	$C_{22}H_{26}N_4O$	72.9	72.85	7.23	7.22	15.46	15.18
C_6H_5	CH_2CH_2OH	A[d,e]	Ethanol	158–160	$C_{16}H_{14}N_2O_2$	72.2	72.4	5.30	5.21	10.5	10.4
4'-ClC_6H_4	CH_2CH_2OH	A[d]	Ethanol	152.5–153.5	$C_{16}H_{13}ClN_2O_2$	63.9	64.0	4.36	4.35	9.3	9.4

[a] DMF = dimethylformamide. [b] KOH in 95% ethanol. [c] Boiled under reflux 1 hr., and the white solid was collected, washed with hot water, and crystallized from benzene. [d] $HOCH_2CH_2NHNH_2$ and the benzophenone-2-carboxylic acid, in a mole ratio of 2:1, respectively, were heated for 30 min. [e] The resulting clear solution was treated with water to give solid crude product.

TABLE II

3-ARYL-3,4-DIHYDRO-(2H)-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES



Ar	Crystn. solvent[a]	M.p., °C.	Formula	—C, %— Calcd.	Found	—H, %— Calcd.	Found	—N, %— Calcd.	Found
C_6H_5	C	137–138	$C_{13}H_{12}N_2O_2S$	60.0	60.2	4.65	4.78		
4-$NO_2C_6H_4$	A	227–230	$C_{13}H_{11}N_3O_4S$	57.2	57.8	3.63	3.72	13.8	13.9
4-$CH_3OC_6H_4$	B	164–165	$C_{14}H_{14}N_2O_3S$	57.9	58.0	4.86	4.80	9.65	9.7
4-$CF_3C_6H_4$	C	239–240	$C_{14}H_{11}F_3N_2O_2S$	51.2	51.5	3.38	3.46	8.5	8.55
4-ClC_6H_4	B	199–201	$C_{13}H_{11}ClN_2O_2S$	53.0	52.9	3.76	3.87	9.5	9.4
3-ClC_6H_4	B	195–198	$C_{13}H_{11}ClN_2O_2S$	53.0	52.9	3.76	4.01	9.5	9.7
4-FC_6H_4	B	186–188	$C_{13}H_{11}FN_2O_2S$	56.1	56.2	3.98	4.10	10.0	10.15
4-$CH_3C_6H_4$	B	168–170	$C_{14}H_{14}N_2O_2S$	61.3	61.2	5.14	5.13	10.2	9.8
4-$(CH_3)_2NC_6H_4$	C	143–144	$C_{15}H_{17}N_3O_2S$	59.4	59.5	5.65	5.69	13.9	13.9
3-NO_2-4-ClC_6H_3	B	200–202	$C_{13}H_{10}ClN_3O_4S$	45.95	45.9	2.97	2.97	12.4	12.0

[a] A = methyl ethyl ketone, B = ethanol, C = 2-propanol.

phenone-2-carboxylic acid[1] (8.5 g., 0.025 mole) and hydrazine (40% w./w. in water, 5 ml.) was heated on a steam bath for 1 hr. The solid mass was triturated with water and then recrystallized from aqueous dimethylformamide to give the phthalazinone (6.7 g., 80%).

Method B. 4-Phenyl-2-(2-dimethylaminoethyl)-1(2H)-phthalazinone.—A mixture of 4-phenyl-1(2H)-phthalazinone (4.4 g., 0.02 mole) and dimethylaminoethyl chloride hydrochloride (3 g., 0.022 mole) in methanol (50 ml.) containing sodium methoxide (2.2 g., 0.04 mole) was heated on a steam bath for 2 hr. Inorganic material was removed by filtration of the chilled mixture and the filtrate was evaporated to dryness. The residue was triturated with 2 *N* HCl and a small amount of starting material was removed. Neutralization gave the phthalazinone, which crystallized from petroleum ether (b.p. 60–80°) as a colorless solid.

2-Chloroethyl-4-phenyl-1(2H)-phthalazinone.—A mixture of 4-phenyl-2-hydroxyethyl-1(2H)-phthalazinone (10 g.), benzene (100 ml.), and $SOCl_2$ (3.5 ml.) was heated under reflux for 3 hr. The solvent was removed *in vacuo*, and the residue crystallized from ethanol as colorless prisms (7.6 g., 71%), m.p. 125–126°.

Anal. Calcd. for $C_{16}H_{13}ClNO$: C, 67.5; H, 4.60; Cl, 12.45; N, 9.8. Found: C, 67.2; H, 4.87; Cl, 12.1; N, 9.6.

2-Aminobenzenesulfonamide.—To a boiling suspension of 2-nitrobenzenesulfonamide[12] (50 g., 0.25 mole) in ethanol was added palladium–charcoal catalyst (1 g., 10% Pd–C) followed by hydrazine hydrate (40 ml., 42% w./w. in water). After the addition was complete the mixture was boiled for 1.5 hr. and cooled, and the catalyst was filtered. The filtrate was evaporated to dryness and the residue was triturated with water to give a buff crystalline solid (39 g., 92.5%), m.p. 156–157° (lit.[11] m.p. 150°). Reduction with iron filings in glacial acetic acid[11] gave a 51% yield of the product and was more difficult to work up.

6-Chlorotoluene-3-sulfonamide.—6-Chloro-3-toluidine (195.8 g., 1.38 moles) was diazotized in glacial acetic acid (2.14 l.) containing concentrated HCl (445 ml.) with sodium nitrite (300 g., dissolved in water). The diazonium solution was added with cooling to a solution of SO_3 in glacial acetic acid (750 ml., 30% w./w. SO_3) containing cuprous chloride (58 g. of Cu_2Cl_2 in 99 ml. of water). The mixture was stirred for a further 2 hr. and then filtered and poured into water, when the crude sulfonyl chloride was precipitated. This could not be crystallized but was converted directly to the sulfonamide by stirring with cold concentrated aqueous ammonia. The amide crystallized from ethanol as colorless prisms (161 g., 61%), m.p. 157.5–159.5°.

Anal. Calcd. for $C_7H_8ClNO_2S$: C, 40.9; H, 3.92; Cl, 17.3; S, 15.6. Found: C, 41.2; H, 3.79; Cl, 17.2; S, 15.6.

N-Acetyl-2-chloro-5-diacetoxymethylbenzenesulfonamide.—To a stirred, cooled (5°) solution of 6-chlorotoluene-3-sulfonamide (167 g., 0.82 mole) in acetic acid (1280 ml.) and acetic anhydride (1270 ml.), concentrated H_2SO_4 (190 ml.) was slowly added followed by finely ground chromium trioxide (224 g.). The resulting mixture was stirred at room temperature for 20 min., then poured onto ice and allowed to stand overnight. The solid was filtered and crystallized from ethyl acetate to give 144 g. (49%) of pure product with m.p. 173–175°.

Anal. Calcd. for $C_{13}H_{14}ClNO_7S$: C, 42.9; H, 3.88; Cl, 9.75; N, 3.85. Found: C, 42.80; H, 4.00; Cl, 9.79; N, 3.81.

From the mother liquors 60 g. of solid was obtained which on crystallization from ethanol gave mixtures of the product and an acid (infrared spectrum). Evaporation of the liquors and

(12) H. E. Fierz-David, E. Schlittler, and H. Waldmann, *Helv. Chim. Acta*, **12**, 663 (1929).

crystallization of the residue from acetic acid gave 5 g. of 3-acetylsulfamyl-4-chlorobenzoic acid, m.p. 235–240°.

Anal. Calcd. for $C_9H_8ClNO_5S$: C, 38.96; H, 2.9; N, 5.05. Found: C, 38.74; H, 2.73; N, 4.86.

2-Chloro-5-formylbenzenesulfonamide.—Ethanol (750 ml.) containing the triacetate VIII (118 g., 0.325 mole) and 350 ml. of 2 *N* HCl was boiled under reflux for 20 min. The ethanol was evaporated under reduced pressure, and the residue was diluted with water to precipitate a colorless solid. Crystallization from 2-propanol gave 31 g. (43.5%) of pure aldehyde with m.p. 169–170°.

Anal. Calcd. for $C_7H_6ClNO_3S$: C, 38.27; H, 2.75; Cl, 16.14; N, 6.38. Found: C, 38.22; H, 3.00; Cl, 16.40; N, 6.18.

Subsequent fractions of crystals from the liquors, although having good melting points (164–167°), were shown by infrared spectra to contain varying proportions of partially hydrolyzed material.

Infrared spectra showed pure aldehyde (Nujol mull): >C=O (1694 cm.$^{-1}$), SO_2NH_2 (1168 and 1330 cm.$^{-1}$), NH_2 (3400, 3370, 3295, and 3220 cm.$^{-1}$); mixtures (Nujol mull): split carbonyl at 1694 (CHO) and 1725 cm.$^{-1}$.

2,4-Dinitrophenylhydrazone, m.p. 301–302°, from dimethylformamide–ethanol.

Anal. Calcd. for $C_{13}H_{10}ClN_5O_6S$: N, 17.6. Found: N, 17.45.

3-(4-Chloro-3-sulfamoylphenyl)-3,4-dihydro-(2H)-1,2,4-benzothiadiazine 1,1-Dioxide.—Diglyme (40 ml.) containing *o*-aminobenzenesulfonamide (3.44 g., 0.02 mole), 2-chloro-5-formylbenzenesulfonamide (4.7 g., 0.02 mole), and 0.2 ml. of ethyl acetate saturated with anhydrous HCl was heated at 90–100° for 4 hr. The resulting solution was cooled and poured onto 200 ml. of water to precipitate a sticky solid. Trituration with ether gave a colorless solid. Repeated crystallization from diglyme–water gave an analytical sample, m.p. 262–264°.

Anal. Calcd. for $C_{13}H_{12}ClN_3O_6S_2$: C, 41.76; H, 3.24; N, 11.24. Found: C, 41.75; H, 3.37; N, 11.00.

Subsequent fractions had m.p. 259–261° which could not be improved. The compounds listed in Table II were prepared by the same general procedure.

Notes

Structures Related to Morphine. XXX.[1] N-Hexyl- and 5-Butyl-, -Amyl-, and -Hexyl-6,7-benzomorphans

BHUWAN C. JOSHI,[2a] COLIN F. CHIGNELL,[2b] AND EVERETTE L. MAY

Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received April 9, 1965

Recently it was reported[3] that optimal analgetic behavior in the 5,9-dialkyl-2′-hydroxy-2′-methyl-6,7-benzomorphan series was shown when the sum of the carbon atoms of these two alkyl substituents was 2–4. It is also known that there is complete loss of activity when the methyl group on the nitrogen of 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan is replaced by ethyl, propyl, or butyl, but that activity is restored when the group on nitrogen becomes amyl.[4] To further define structural limits at the 2(nitrogen)- and 5-positions, 2-hexyl-2′-hydroxy-α-5,9-dimethyl-6,7-benzomorphan (III)[5] and 5-butyl-, -amyl-, and -hexyl-2′-hydroxy-2-methyl-6,7-benzomorphans (II) have been synthesized, assessed for analgetic activity, and compared with the lower homologs.

The method of synthesis used for II *via* I was a modification of the Stevens rearrangement and has been described before[3,6] for various analogs. Acid cyclization of I proceeded in much lower yields than was the case with lower homologs[3,6] and with 3,4-dialkyl-1,2,5,6-tetrahydropyridines when the alkyl group at position 4 was methyl to propyl.[3,6,7] Phosphoric acid (85%) at 150–160° proved superior to boiling 48% HBr.

Compound IIIa was synthesized from 2′-methoxy-α-2,5,9-trimethyl-6,7-benzomorphan essentially as described for lower N-alkyl homologs.[4a] Benzomorphan Ia was converted to the methyl ether (with diazomethane) which, as the methiodide, was cleaved to 1,2-dihydro(2-dimethylaminoethyl)-1-hexyl-7-methoxynaphthalene with hot, aqueous NaOH. This methine was hydrogenated to the corresponding tetrahydronaphthalene which was tested for diuretic activity.[8]

As shown in Table I, in the 5-alkyl series, compounds IIe, IIf, and IIa are equipotent and comparable to morphine.[9] Activity begins to drop with amyl (IIb) and decreases sharply with hexyl (IIc) which is almost identical with the 5-methyl homolog (IId). Thus, like the 5,9-dialkyl series, maximum activity obtains when the carbon total numbers 2–4. In contrast,

TABLE I

ANALGETIC ACTIVITY OF 5-ALKYL-2′-HYDROXY-2-METHYL-6,7-BENZOMORPHANS (II) AND OF α-2-ALKYL-2′-HYDROXY-5,9-DIMETHYL-6,7-BENZOMORPHANS (III)

II			III		
No.	R	ED_{50}[a]	No.	R	ED_{50}[a]
IId	Me	10.4[b]	IIIb	Me	3.0[b]
IIe	Et	2.3[b]	IIIc	Et	I[c]
IIf	Pr	2.1[b]	IIId	Pr	I[c]
IIa	Bu	2.0	IIIe	Bu	I[c]
IIb	Am	3.4	IIIf	Am	2.1[d]
IIc	Hex	10.8	IIIa	Hex	1.5
Morphine		2.1			

[a] Expressed in mg./kg. of hydrochloride salt (mice, subcutaneous administration): see N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). [b] See ref. 3. [c] Inactive; see ref. 4. [d] See ref. 4.

(1) Previous paper: C. F. Chignell and E. L. May, *J. Med. Chem.*, **8**, 385 (1965).

(2) (a) Visiting Scientist from Allahabad University, India. (b) Visiting Fellow from the Chelsea School of Pharmacy, London, England.

(3) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

(4) (a) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960); (b) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 125 (1964), have found that the N-propyl compound is one of the most potent morphine antagonists known.

(5) For proof of configuration at position 9 and an explanation of the α- and β-designations, see S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(6) (a) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961); (b) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

(7) J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *ibid.*, **28**, 2470 (1963).

(8) By Smith Kline and French Laboratories.

(9) Considering optical activity, morphine is only half as potent on the reasonable assumption that most of the activity of II (racemates) resides in one antipode.