of $NaNO_2$ in 36 ml. of water. To the resulting solution was then added a solution of 80 g. of SO_2 in 240 ml. of acetic acid to which had been added a solution of 12 g. of cuprous chloride dihydrate in 21 ml. of water. The mixture was stirred for 1 hr., then poured into an excess of ice water. The precipitated yellow solid was separated, washed with water, then added to 210 ml. of concentrated NH_4OH. This mixture was stirred for 1 hr. and allowed to stand overnight. The resulting solid was recrystallized from ethanol to give fine, yellow needles, m.p. 191–192°.

Anal. Calcd. for $C_8H_8N_2O_3S$: C, 48.97; H, 4.11; N, 14.28; S, 16.34. Found: C, 49.13; H, 4.69; N, 13.71; S, 16.24.

N-Hydroxy-4-bromobenzenesulfonamide (XVII).—A cold solution of 11.5 g. (0.51 g.-atom) of sodium in 150 ml. of absolute ethanol was added, at such a rate that no boiling occurred, to a stirred, hot solution of 32.5 g. (0.47 mole) of hydroxylamine hydrochloride in 12 ml. of water. After the addition, NaCl was removed by filtration and washed with 150 ml. of absolute ethanol. The stirred filtrate and washings were then treated, portionwise, with 36.2 g. (0.14 mole) of 4-bromobenzenesulfonyl chloride, stirred for 1 hr., then evaporated under reduced pressure. The residue was extracted with ether and the ether solution was evaporated. Recrystallization from water gave 15 g. (42%) of white prisms, m.p. 146–147°.

Anal. Calcd. for $C_6H_6BrNO_3S$: C, 28.58; H, 2.40; Br, 31.70; N, 5.56; S, 12.72. Found: C, 28.34; H, 2.39; Br, 31.72; N, 5.38; S, 12.84.

N-Methoxy-4-bromobenzenesulfonamide (XVIII).—A solution of 8.8 g. (0.22 mole) of NaOH in 100 ml. of water and 150 ml. of ethanol was treated with 16.6 g. (0.2 mole) of methoxyamine hydrochloride and 25.6 g. (0.1 mole) of 4-bromobenzenesulfonyl chloride, then stirred and heated under reflux for 2 hr. The cooled mixture was poured into 2.5 l. of ice water and the precipitated solid was recrystallized from aqueous ethanol to give 18.5 g. (70%) of white needles, m.p. 98–100°.

Anal. Calcd. for $C_7H_8BrNO_3S$: C, 31.39; H, 3.03; Br, 30.03; N, 5.26; S, 12.05. Found: C, 31.53; H, 3.12; Br, 29.90; N, 5.12; S, 12.31.

N-Methyl-N-hydroxy-4-bromobenzenesulfonamide (XIX).—This substance was made by the same method used for **18** above, using N-methylhydroxylamine hydrochloride. Recrystallization from aqueous ethanol gave 11.0 g. (41%) of white needles, m.p. 122–124°.

Anal. Calcd. for $C_7H_8BrNO_3S$: C, 31.59; H, 3.03; Br, 30.03; N, 5.26; S, 12.05. Found: C, 31.62; H, 3.14; Br, 29.98; N, 5.39; S, 12.23.

N-Allyl-4-bromobenzenesulfonamide (XXIII).—A mixture of 11.4 g. (0.2 mole) of allylamine and 25.6 g. (0.1 mole) of the 4-bromobenzenesulfonyl chloride in 350 ml. of benzene was stirred for 1 hr., then evaporated under reduced pressure. The dark residue was triturated with water and recrystallization from aqueous ethanol, using Darco G-60, to give 16.8 g. (61%) of white needles, m.p. 64–65°.

Anal. Calcd. for $C_9H_{10}BrNO_2S$: C, 39.14; H, 3.65; Br, 28.94; N, 5.07; S, 11.61. Found: C, 39.25; H, 3.82; Br, 28.63; N, 5.06; S, 11.69.

N-(3-Pyridyl)-4-bromobenzenesulfonamide (XXIX).—A mixture of 25.5 g. (0.1 mole) of 4-bromobenzenesulfonyl chloride, 18.8 g. (0.2 mole) of 3-aminopyridine, and 350 ml. of water was brought to a boil, then allowed to cool and stand overnight. The precipitated solid was recrystallized from aqueous acetone, using Darco G-60, to give 14 g. (45%) of white crystals, m.p. 187–188°.

Anal. Calcd. for $C_{11}H_9BrN_2O_2S$: C, 42.18; H, 2.90; Br, 25.52; N, 8.95; S, 10.24. Found: C, 42.27; H, 2.66; Br, 25.66; N, 8.47; S, 10.28.

N-(4-Pyridyl)-4-bromobenzenesulfonamide (XXX).—This substance was prepared in the same manner as **29**, using 4-aminopyridine. Recrystallization of the precipitated solid from aqueous dimethylformamide gave 13 g. (42%) of white plates, m.p. 325–326° dec.

Anal. Calcd. for $C_{11}H_9BrN_2O_2S$: C, 42.18; H, 2.90; Br, 25.52; N, 8.95; S, 10.24. Found: C, 42.36; H, 2.76; Br, 25.41; N, 8.71; S, 10.16.

N-Methyl-N¹-(4-bromobenzenesulfonyl)piperazine (XXXIV).—A mixture of 22 g. (0.22 mole) of N-methylpiperazine, 350 ml. of benzene, and 25.6 g. (0.1 mole) of 4-bromobenzenesulfonyl chloride was stirred for 4 hr., diluted with 500 ml. of benzene, washed with 120 ml. of 10% aqueous NaOH, dried ($MgSO_4$), and evaporated. Recrystallization of the residue from absolute ethanol gave 23.8 g. (75%) of white needles, m.p. 153–154°.

Anal. Calcd. for $C_{11}H_{15}BrN_2O_2S$: C, 41.38; H, 4.74; Br, 25.03; N, 8.78; S, 10.05. Found: C, 41.62; H, 4.64; Br, 25.05; N, 8.80; S, 10.08.

Acknowledgments.—Grateful acknowledgment is made to D. B. Hooker, R. R. Russell, H. J. Triezenberg, and D. M. Devendorf for excellent technical assistance, and to J. B. Wright for compounds **12** and **13.**

New Compounds

Some 2,3,6-Trisubstituted Quinazolones

K. KISHOR, R. C. ARORA, AND SURENDRA S. PARMAR[1]

Department of Pharmacology and Therapeutics, K. G. Medical College, Lucknow University, Lucknow, India

Received November 2, 1964

In a series of ring-substituted benzylamines synthesized with regard to all possible electron distribution in the benzene ring by induction and resonance, Zeller[2] reported that *m*-iodobenzylamine was found to be 2–3 times better as a substrate for beef liver monoamine oxidase than benzylamine. We have now synthesized some iodo-substituted quinazolones from aliphatic and as well as aromatic amines in continuation of our work on the synthesis of 2,3-disubstituted quinazolones.[3] Such quinazolones have been reported to possess hypnotic[4] and anticonvulsant[5] properties. In the present study, 2,3-disubstituted 6-iodoquinazolones were synthesized following the method of Bogert, *et al.*[6]

Experimental[7]

Quinazolones. General Procedure.—Iodoacetanthranil (m.p. 150–154°) was synthesized by refluxing 5 g. of 5-iodoanthranilic acid[8] with 50 ml. of acetic anhydride for 1 hr. After distilling the excess acetic anhydride, 6-iodoacetanthranil separated out as a solid mass in 60–65% yield (*Anal.* Calcd. for $C_9H_6INO_2$: C, 37.6; H, 2.09; N, 4.8. Found: C, 37.1; H, 2.0; N, 4.48.) and was used without further purification. Molar proportions of 6-iodoacetanthranil and the appropriate amines were mixed together for the preparation of quinazolones as reported earlier.[3] The 2,3-disubstituted 6-iodoquinazolones, summarized in Table I, were characterized by their sharp melting points and by analyses.

(1) The authors wish to express their thanks to Professor T. R. Govindachari, Director, Ciba Research Laboratories, Bombay, India, for the microanalyses of the compounds and to the State Medical Research Council (U. P.) for a research grant and providing a research fellowship to R. C. Arora.

(2) E. A. Zeller, *Ann. N. Y. Acad. Sci.*, **107**, 811 (1963).

(3) K. Kishor, R. Kumar, and S. S. Parmar, *J. Med. Chem.*, **7**, 851 (1964).

(4) M. L. Gujral, R. P. Kohli, and P. N. Saxena, *J. Assoc. Physicians*, II, 29 (1955).

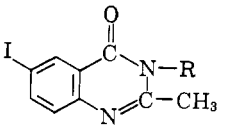
(5) M. L. Gujral, P. N. Saxena, and R. P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).

(6) T. A. Williamson in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., London, 1957, pp. 324–376.

(7) Melting points were taken in a capillary tube and are corrected.

(8) C. J. Klemme and J. H. Hunter, *J. Org. Chem.*, **5**, 227 (1940).

TABLE I
2-METHYL-3-R_1-6-IODO-4-QUINAZOLONE



R_1	M.p., °C.[b]	Yield, %	Formula	Crystn. solvent	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
Phenyl[a]	151.2 (151–152)	50	$C_{15}H_{11}IN_2O$	EtOH	49.7	3.03	7.03	49.3	3.0	7.4
Benzyl	(121–123)	75	$C_{16}H_{13}IN_2O$	EtOH	51.06	3.03	7.4	51.0	3.2	7.8
o-Tolyl[a]	137.8–139.6 (142–144)	70	$C_{16}H_{13}IN_2O$	EtOH–H_2O	51.06	3.4	7.4	51.1	3.6	7.5
m-Tolyl[a]	177–179 (179–181)	60	$C_{16}H_{13}IN_2O$	EtOH–H_2O	51.06	3.4	7.4	50.9	3.2	7.3
o-Anisyl[a]	177–179 (178–180)	50	$C_{16}H_{13}IN_2O_2$	EtOH	48.98	3.31	7.13	48.64	3.01	7.2
m-Anisyl	175–177	45	$C_{16}H_{13}IN_2O_2$	EtOH	48.98	3.31	7.13	48.73	3.45	7.4
α-Naphthyl	155–157	55	$C_{19}H_{14}IN_2O$	EtOH	55.34	3.16	6.7	55.64	3.53	6.5
β-Naphthyl	253.5	55	$C_{19}H_{14}IN_2O$	EtOH	55.34	3.16	6.7	55.85	3.18	6.2
o-Aminophenyl	>290	30	$C_{15}H_{13}IN_3O$	EtOH–AcOH	47.8	3.18	11.1	47.3	3.09	11.45
p-Aminophenyl	>290	40	$C_{15}H_{13}IN_3O$	EtOH–AcOH	47.8	3.18	11.1	47.5	3.23	11.0
Isopropyl	177–178	40	$C_{12}H_{13}IN_2O$	EtOH	43.9	4.0	8.5	43.6	4.4	8.4
2-Hydroxyethyl	177–179	40	$C_{11}H_{11}IN_2O_2$	EtOH	40.00	3.8	8.4	39.8	3.7	8.9
n-Butyl	114–116	45	$C_{13}H_{15}IN_2O$	EtOH	43.9	4.00	8.5	43.5	3.9	8.2
Anilino	217.5	35	$C_{15}H_{12}IN_3O$	AcOH–C_6H_6	47.7	3.1	11.1	47.5	3.0	11.5
p-Nitrophenyl[a]	207–209 (209–210)	60	$C_{15}H_{11}IN_3O_3$	EtOH	44.2	2.4	10.3	44.00	2.7	10.2
2,4-Dinitroanilino	171–172	30	$C_{15}H_{10}IN_5O_5$	C_6H_6	38.5	2.71	14.9	38.2	2.5	14.8
2-Pyridyl	166–168	70	$C_{14}H_{12}IN_4O$	EtOH	46.3	2.7	11.56	46.11	2.5	11.55
3-Methyl-2-pyridyl	159–161	70	$C_{15}H_{14}IN_4O$	EtOH	49.5	3.3	7.7	49.3	3.00	7.6

[a] These compounds have been synthesized earlier by a different synthetic method. [b] Figures in parentheses are the melting points reported in the literature.

Derivatives of Fluorene. XX.[1a,b] Fluorofluorenes. V. New Difluoro-2-acetamidofluorenes for the Study of Carcinogenic Mechanisms

MOSES J. NAMKUNG, T. LLOYD FLETCHER,[1c] AND WILLIAM H. WETZEL

Chemistry Research Laboratory of the Department of Surgery, University of Washington School of Medicine, Seattle, Washington 98105

Received March 9, 1965

Six monofluoro-2-acetamidofluorenes (2-AAF)[2] and the first two (1,7 and 3,7) difluoro-2-AAF have been reported.[3] Results of testing of some of these substances, by Miller and Miller of the McArdle Memorial Laboratory, and reasons for testing these substances have been published.[4]

We here describe preparation of three new (4,7, 5,7, and 6,8) difluoro-2-AAF and related compounds. The first two have fluorine in the 7-position which markedly enhances liver carcinogenicity of 2-AAF[5] perhaps by blocking a detoxification site, perhaps also by altering the potency of the N-hydroxy metabolite which is more carcinogenic than the AAF itself.[6]

Since some polychlorofluorenes show antitumor effects, a few of the present compounds were tested by the CCNSC, but the results indicate that none of them has cytotoxic effects.

Experimental[7]

2,5-Difluorofluorenone.—To 42.6 g. (0.2 mole) of 5-fluoro-9-oxo-2-fluorenamine[2b] in 100 ml. of dimethyl sulfoxide,[8] 200 ml. of 48% fluoroboric acid was added with stirring. After cooling to 0°, a saturated solution of 21 g. (0.3 mole) of $NaNO_2$ was added slowly. After stirring for 30 min., the salt was filtered off, washed with 20 ml. of 5% fluoroboric acid, 20 ml. of methanol, and 20 ml. of ether, and dried giving 58 g. (93%) of salt, dec pt. 180°. This was decomposed in 500 ml. of boiling *o*-dichlorobenzene which was boiled down to near dryness, 100 ml. of benzene was added, and the mixture was filtered. Upon cooling, a precipitate was filtered off, giving 31 g. (72%) of product, m.p. 142–144°. Recrystallization from ethanol raised the melting point to 146–147°. An analytical sample was prepared by sublimation at 140° (1 mm.); m.p. 147–147.5°; ν_{max} 1721 (keto C=O), 1274, 1233 (C–F stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.44; H, 2.80; F, 17.22.

4,7-Difluoro-2-nitrofluorenone.—To 60 ml. of HNO_3 (90%), 31 g. (0.144 mole) of 2,5-difluorofluorenone was added in portions with stirring and cooling (below 30°). The mixture was removed from the ice bath, and with continued stirring, the temperature

(1) (a) This work was supported in part by a grant (CA-01744) from the National Cancer Institute and, in part, by a Career Development Award 5K3-GM-14,991 to T. L. F. (b) For Part XIX see T. L. Fletcher, M. J. Namkung, J. R. Dice, and S. K. Schaefer, *J. Med. Chem.*, **8**, 347 (1965). (c) To whom requests for reprints should be addressed.

(2) (a) T. L. Fletcher, W. H. Wetzel, M. J. Namkung, and H. L. Pan, *J. Am. Chem. Soc.*, **81**, 1092 (1959); (b) T. L. Fletcher, M. J. Namkung, H. L. Pan, and W. H. Wetzel, *J. Org. Chem.*, **25**, 996 (1960); (c) T. L. Fletcher, M. J. Namkung, W. H. Wetzel, and H. L. Pan, *ibid.*, **25**, 1342 (1960).

(3) M. J. Namkung and T. L. Fletcher, *ibid.*, **26**, 2243 (1961).

(4) E. C. Miller, T. L. Fletcher, A. Margreth, and J. A. Miller, *Cancer Res.*, **22**, 1002 (1962).

(5) J. A. Miller, R. B. Sandin, E. C. Miller, and H. P. Rusch, *ibid.*, **15**, 188 (1955).

(6) E. C. Miller, J. A. Miller, and H. A. Hartmann, *ibid.*, **21**, 815 (1961).

(7) Melting points, except those above 300°, are corrected to standards and were taken on a Fisher-Johns block. The infrared spectra were taken in KBr disks with a Beckman IR-5 at a concentration of *ca.* 1.5 mg./300 mg. of KBr. Band assignments for C–F stretching are tentative and a continuation of earlier data.[2c] Analyses were run by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr), Germany.

(8) T. L. Fletcher and M. J. Namkung, *Chem. Ind.* (London), 179 (1961).