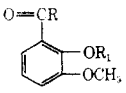
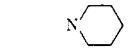
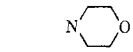
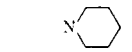
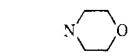
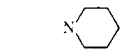
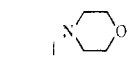
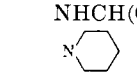
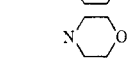
TABLE I

AMIDES OF 2-HYDROXY- (OR ALKOXY-) 3-METHOXYBENZOIC ACID



No.	R	R_1	Formula[a]	Mp or bp, (mm) °C	Yield,[c] %	Recrystn[d] solvent
1	NH_2	CH_3	$C_9H_{11}NO_3$	93–94	78	EtOH
2	$N(CH_3)_2$	CH_3	$C_{11}H_{15}NO_3$	206–208 (35)	66	
3	$N(C_2H_5)_2$	CH_3	$C_{13}H_{19}NO_3$	175–178 (10)	71	
4	$NHCH(CH_3)_2$	CH_3	$C_{12}H_{17}NO_3$	183–185 (13)	70	
5		CH_3	$C_{14}H_{19}NO_3$	178–180 (10)	64	
6		CH_3	$C_{13}H_{17}NO_4$	87–88	71	EtOH
7	$NHCH_2C_6H_5$	CH_3	$C_{16}H_{17}NO_3$	71–72	76	EtOH
8	NH_2	C_2H_5	$C_{10}H_{13}NO_3$	121–122	85	EtOH
9	$N(CH_3)_2$	C_2H_5	$C_{12}H_{17}NO_3$	174–176 (11)	72	
10	$N(C_2H_5)_2$	C_2H_5	$C_{14}H_{21}NO_3$	184–186 (13)	83	
11	$NHCH(CH_3)_2$	C_2H_5	$C_{13}H_{19}NO_3$	178–180 (14)	68	
12		C_2H_5	$C_{15}H_{21}NO_3$	204–206 (11)	89	
13		C_2H_5	$C_{14}H_{19}NO_4$	89–90	90	EtOH
14	$NHCH_2C_6H_5$	C_2H_5	$C_{17}H_{19}NO_3$	79–80	77	EtOH
15	NH_2	$CH(CH_3)_2$	$C_{11}H_{15}NO_3$	157–158	87	EtOH
16	$N(CH_3)_2$	$CH(CH_3)_2$	$C_{13}H_{19}NO_3$	168–170 (16)	60	
17	$N(C_2H_5)_2$	$CH(CH_3)_2$	$C_{15}H_{23}NO_3$	172–174 (10)	64	
18	$NHCH(CH_3)_2$	$CH(CH_3)_2$	$C_{14}H_{21}NO_3$	175–177 (10)	61	
19		$CH(CH_3)_2$	$C_{16}H_{23}NO_3$	213–215 (14)	84	
20		$CH(CH_3)_2$	$C_{15}H_{21}NO_4$	203–205 (12)[b]	82	
21	$NHCH_2C_6H_5$	$CH(CH_3)_2$	$C_{18}H_{21}NO_3$	58–59	60	E–PE
22	$N(C_2H_5)_2$	H	$C_{12}H_{17}NO_3$	85–86	64	E–PE
23	$NHCH(CH_3)_2$	H	$C_{11}H_{15}NO_3$	127–128	68	E–EtOH
24		H	$C_{13}H_{17}NO_3$	120–121	70	E–EtOH
25		H	$C_{12}H_{15}NO_4$	108–109	69	E–EtOH

[a] All compds were analyzed for C, H, N. [b] Also mp 56–57°. [c] Purified compds. [d] E, ether; PE, petroleum ether (35–45°).

continued 50 min after completion of the addition at room temp. $Et_3N \cdot HCl$ was removed by filtration and the filtrate was evapd to dryness. To the dry residue was added 5 g of Na_2CO_3 in 50 ml of H_2O (if necessary a few ml of EtOH was added) and the mixture was refluxed for 2 hr. After cooling, the soln was made strongly alkaline with 10% KOH, the mixture was washed with $CHCl_3$, acidified, and extd with $CHCl_3$ and the solvent was evaporated to dryness. Yields and physical constants are given in Table I.

Carcinogenic Activity of Dibenzothiophene Analogs of *p*-Dimethylaminoazobenzene

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Our previous work[1] has shown that replacement of the unsubstituted ring of *p*-dimethylaminoazobenzene (DAB) with heterocyclic rings lead to a number of very active carcinogens and shows some interesting variations among isomers. Now we wish to report the preparation and testing for rat hepatocarcinogenic action of the four isomeric *p*-dimethylaminophenylazodibenzothiophenes (Table I).

TABLE I

N,N-DIMETHYL-*p*-X-DIBENZOTHIENYLANILINE

X[a]	Yield, %	Mp, °C
1	38.6	170–176
2	57.2	184–187
3	20.6	219–220
4	43.5	163–164

[a] All compounds ($C_{20}H_{17}N_3S$) were analyzed for C, H, and N and the results were within ±0.4% of the theoretical value.

Experimental Section[2]

All of the azo compounds were prepared by coupling $PhNMe_2$ with the appropriate aminodibenzothiophenes. A typical procedure is given below. 1- and 2-aminodibenzothiophene were prepared by the procedures developed by Gilman and coworkers[3–5]

* To whom correspondence should be addressed.

(1) E. V. Brown and W. M. Fisher, *J. Med. Chem.*, **12**, 1113 (1969).

(2) All melting points were determined on a Fisher-Johns apparatus and are corrected. The C, H analyses were performed in this department on an F and M Model 185 analyzer by Mr. Daryl Sharp.

(3) H. Gilman and J. F. Nobis, *J. Amer. Chem. Soc.*, **71**, 274 (1949).

(4) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(5) H. Gilman and G. R. Welder, *J. Amer. Chem. Soc.*, **76**, 2906 (1954).

and Kornblum.[6] 4-Aminodibenzothiophene was obtained from the Hoffman rearrangement as described by Gilman.[7] 3-Aminodibenzothiophene was prepared by nitration of dibenzothiophene 5-oxide and subsequent reduction.[8]

N,N-Dimethyl-p-(1-dibenzothienyl)aniline.—To a suspension of 8.00 g of 1-aminodibenzothiophene in 120 ml of 1:3 $EtCO_2H$–AcOH at 0–5° was added 20 ml of nitrosylsulfuric acid (from 3.08 g of $NaNO_2$ to 20 ml of H_2SO_4 at 75–80°) dropwise with vigorous stirring. The suspension was allowed to stir for 20 min before addn of 2 g of urea to destroy any excess HNO_2. To the cold diazonium soln was added a cool soln of 5.2 ml of $PhNMe_2$ in 20 ml of 1:3 $EtCO_2H$–AcOH. NH_4OAc was added slowly until the suspension no longer changed congo red paper. The suspension was stirred for 1 hr at 5° after which it was poured into 1 l. of ice water and filtered. The solid was dissolved in $CHCl_3$, dried ($MgSO_4$), and dild with an equal vol of Skelly C. This soln was chromatographed on a 60 cm × 3 cm alumina column packed in PhMe. The dye was eluted with 2:1 Skelly C–$CHCl_3$ and recrystd once from cyclohexane and once from Skelly C to give a fine red solid, mp 170–176°.

In the biological evaluation[9] DAB (Butter yellow) at the 0.06% level gave tumor incidences of 7/10 at 4 months and 9/10 at 6 months. All 4 isomers of N,N-dimethyl-p-(dibenzothienyl)aniline proved inactive when tested at the 0.06% level in the same manner for 6 months.

Acknowledgment.—The authors are indebted to Dr. Daniel L. Weiss and Dr. T. Yoneyama, Department of Pathology, University of Kentucky College of Medicine, for the microscopic evaluation of the tumors.

(6) E. C. Horning, Ed., "Organic Synthesis," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 295.

(7) H. Gilman and D. L. Esmay, *ibid.*, **74**, 2021 (1952).

(8) R. K. Brown, R. G. Christiansen, and R. B. Sandin, *J. Amer. Chem. Soc.*, **70**, 1748 (1948).

(9) E. V. Brown and C. J. Sanchorawola, *J. Med. Chem.*, **11**, 1074 (1968).

Heterocycles. 4. Syntheses of Benzo[h]quinoline Derivatives[1]

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During an attempted synthesis of heterocyclic steroids,[2] some derivatives of benzo[h]quinoline were synthesized and are reported here. The method of synthesis is analogous to the route used by Bachmann, *et al.*,[3] for the preparation of equilenin.

* To whom correspondence should be addressed.

(1) Part III: T. Moriwake and H. Namba, *J. Med. Chem.*, **11**, 636 (1968).

(2) P. Morand and J. Lyall, *Chem. Rev.*, **67**, 85 (1967).

(3) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Amer. Chem. Soc.*, **62**, 824 (1940).

Experimental Section[4]

Methyl 4-Oxo-1-tosyl-1,2,3,4-tetrahydrobenzo[h]quinoline-3-glyoxalate (I).—A mixture of 3.0 g of NaOMe and 5.0 g of dimethyl oxalate in 40 ml of C_6H_6 was refluxed for 10 min. To the cooled soln was added a soln of 7.0 g of 4-oxo-N-tosyl-1,2,3,4-tetrahydrobenzo[h]quinoline[5] in 50 ml of THF, the mixture was stirred at room temperature for 15 hr, and hydrolyzed with H_2O. The organic layer which sepd was extd with 5% NaOH soln and the combined aq soln was acidified with dil HCl. The yellow crystals were filtered off and dried. Recrystn from MeOH–Me_2CO (1:1) gave 6.6 g (75.4%) of pure I: mp 156–157°; ir (Nujol) 1740 cm^{-1}. *Anal.* ($C_{23}H_{19}NO_6S$) C, H, N.

Methyl 4-Oxo-1-tosyl-1,2,3,4-tetrahydrobenzo[h]quinoline-3-carboxylate (II).—A mixture of 4.0 g of I and 2.0 g of powdered glass was heated at 180° for 30 min. After cooling, the dark product was dissd in Me_2CO and the soln was decanted from the glass, treated with charcoal and allowed to evapd. Recrystn of the residue from MeOH gave 2.7 g (75.2%) of pure II: mp 154–155°; ir (Nujol) 1645 cm^{-1}. *Anal.* ($C_{22}H_{19}NO_5S$) C, H, N.

Methyl 3-Methyl-4-oxo-1-tosyl-1,2,3,4-tetrahydrobenzo[h]-quinoline-3-carboxylate (III).—To a soln of 1.0 g of Na in 20 ml of MeOH was added a soln of 3.0 g of II in 20 ml of MeOH and 20 ml of C_6H_6. The mixture was refluxed for 15 min, cooled, and treated with 3 ml of MeI. After 30 min at room temp, an addl 3 ml of MeI was added. The mixture was stirred at room temp for 2 hr, then refluxed for 45 min, cooled, neutralized with AcOH, and evapd nearly to dryness. The residue was extd with a mixture of C_6H_6 and Et_2O. The organic soln was washed with dil aq NaOH and H_2O, dried, and evapd to give 1.5 g (48.4%) of crude product, mp 128–137°. Recrystn from MeOH gave 1.0 g (32.3%) of pure III: mp 185–186°; ir (Nujol) 1735, 1675 cm^{-1}. *Anal.* ($C_{23}H_{21}NO_5S$) C, H, N.

From the mother liquid, a small amount of **methyl 1,2-dihydro-4-methoxy-1-tosylbenzo[h]quinoline-3-carboxylate** was obtd: mp 113–114.5°; ir (Nujol) 1700 cm^{-1}. *Anal.* ($C_{23}H_{21}NO_5S$) C, H, N.

Methyl 10,11-Dihydro-10-tosyl-2H-benzo[h]pyrazolo[4,3-c]-quinoline-1-carboxylate (IV).—A mixture of 5.0 g of I, 15 ml of AcOH, and 3.0 g of hydrazine hydrate was refluxed for 1 hr. After cooling, the sepd cryst was filtered off and was recrystd from MeOH–Me_2CO (1:1) to give 3.9 g (78.8%) of crude IV; mp 222–226°. Further recrystn from MeOH-Me_2CO (1:1) gave a pure sample of IV: mp 239–240°; ir (Nujol) 3275, 1720 cm^{-1}. *Anal.* ($C_{23}H_{19}N_3O_4S$) C, H, N.

10,11-Dihydro-11a-methyl-1-oxo-10-tosyl-2H-benzo[h]-pyrazolo[4,3-c]quinoline (V).—A mixture of 1.0 g of III, 75 ml of EtOH, and 1.0 g of hydrazine hydrate was refluxed for 4 hr. After cooling, the sepd cryst were filtered off, washed (H_2O), and dried *in vacuo*. Recrystn from MeOH gave 0.1 g of pure V: mp 232–234°; ir (Nujol) 3250 and 1700 cm^{-1}. *Anal.* ($C_{22}H_{19}N_3O_3S$) C, H, N.

Reaction of II with hydrazine hydrate under various conditions gave no condensn prod.

(4) All melting points are uncorrected. Microanalyses were performed by Mr. E. Amano. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

(5) W. N. Speckamp and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **85**, 671 (1966).