(6) M. P. Cava and N. Srinivasan, *Tetrahedron*, **26**, 4649 (1970).
(7) (a) U. Ungerstedt, *Eur. J. Pharmacol.*, **5**, 107 (1968); (b) U. Ungerstedt and G. W. Arbuthnott, *Brain Res.*, **24**, 485 (1970).
(8) (a) N. E. Andén, S. G. Butcher, and J. Engel, *J. Pharm. Pharmacol.*, **22**, 548 (1970); (b) U. Ungerstedt, K. Fuxe, M. Goldstein, A. Battista, M. Ogawa, and B. Anagnoste, *Eur. J. Pharmacol.*, **21**, 230 (1973).
(9) W. S. Saari, S. W. King, and V. J. Lotti, *J. Med. Chem.*, **16**, 171 (1973).
(10) M. V. Koch, J. G. Cannon, and A. M. Burkman, *J. Med. Chem.*, 11, 977 (1968).
(11) R. I. Schoenfeld, J. L. Neumeyer, W. Dafeldecker, and S. Roffler-Tarlov, *Eur. J. Pharmacol.*, in press.
(12) S. Lal, T. L. Sourkes, K. Missala, and G. Belendiuk, *Eur. J. Pharmacol.*, **20**, 71 (1972).
(13) R. V. Smith and M. R. Cook, *J. Pharm. Sci.*, **63**, 161 (1974).
(14) R. N. Iyer, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res., Sect. C*, **16**, 157 (1957).
(15) L. Feiser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1955, p 345.
(16) J. Weinstock and V. Bolkelheide, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 641.

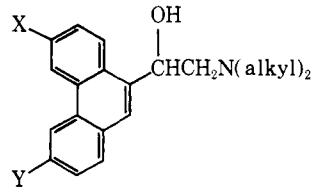
Synthesis and Antimalarial Evaluation of 9,10-Dihydrophenanthrene Amino Alcohols†

Adrienne S. Dey and John L. Neumeyer*

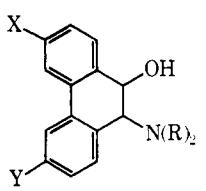
Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received March 4, 1974*

A new series of 9-alkylamino-9,10-dihydro-10-hydroxyphenanthrenes and 9-alkylaminophenanthrenes has been prepared. Compounds of this series are related to the phenanthrene amino alcohols which have been known to be active antimalarials and are distinguished in possessing a biphenyl ring system bearing an α-hydroxy-β-substituted amino side chain in place of the 9-substituted phenanthrene ring bearing an α-hydroxy-ω-alkylamino side chain. The compounds were inactive and nontoxic in the antimalarial screen. The compounds were synthesized through the 9,10-epoxy-9,10-dihydrophenanthrenes **11**, one of which (**11c**) showed a mean survival time of 4 days at 640 mg/kg in mice infected with *Plasmodium berghei*.

The phenanthrene amino alcohols **1** are a class of active antimalarial compounds which emerged during World War II and have been actively reinvestigated in the current antimalarial programs.[1,2] Our rationale for the synthesis of compounds of type **2** was based on the structural analogy of **2** to the active phenanthrene-type antimalarials of type **1**. Numerous structure–activity studies encom-



1, X, Y = Cl, Br, CF_3, H



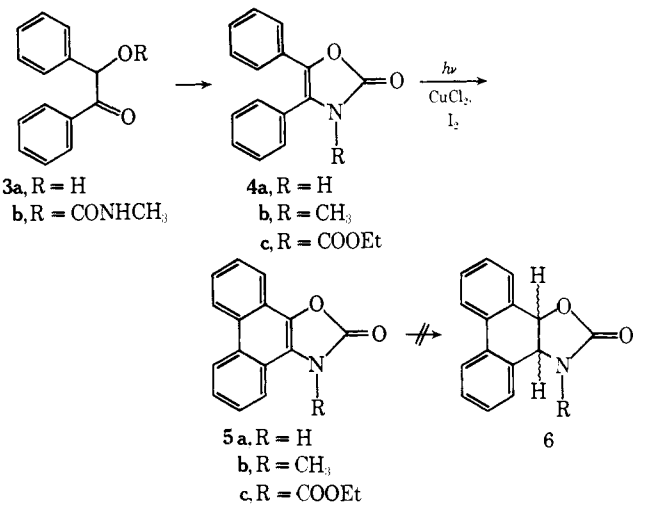
2, X, Y = H, CF_3, Br

passing many hundreds of individual drugs have demonstrated that arylamino alcohol antimalarials of maximum activity require a polycyclic aromatic ring system bearing an α-hydroxy-ω-(alkyl-substituted)amino side chain and additional electron-withdrawing hydrophobic substituents. We wished to assess the structural requirements of such arylamino alcohols by preparing a series of 9-amino-10-hydroxy-9,10-dihydrophenanthrenes. In the series (Table I) reported in this paper, the polycyclic aromatic ring system can be considered as a substituted biphenyl system bearing an α-hydroxy-β-substituted bridge. The biological activity of these compounds against *Plasmodium berghei* infections in mice and *Plasmodium gallinaceum* infections in chicks was determined.

Chemistry. Our initial approach[3] to the synthesis of such 9,10-dihydrophenanthrenes **2** involved a photochemical cyclization of a substituted stilbene incorporating the 4-oxazolin-2-one ring system (Scheme I). Although successful in producing the substituted phenanthrene (**5**), this method did not prove advantageous for the synthesis of the desired compounds.

† This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DADA 17-70-C-0095. This paper is Contribution No. 1255 from the Army Research Program on Malaria.

Scheme I



3a, R = H
b, R = $CONHCH_3$

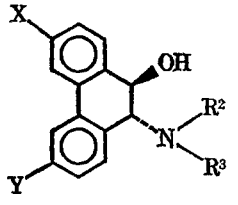
4a, R = H
b, R = CH_3
c, R = COOEt

5a, R = H
b, R = CH_3
c, R = COOEt

6

Benzoin (**3a**) and methyl isocyanate in the presence of pyridine were caused to react to give the carbamate **3b** which in refluxing glacial acetic acid yielded 3-methyl-4,5-diphenyloxazolin-2-one (**4b**).[4] **4b** could also be prepared by the N-alkylation of **4a** with sodium hydride and methyl iodide in DMF. 3-Carbethoxy-4,5-diphenyloxazolin-2-one (**4c**) was similarly prepared from **4a** and ethyl chloroformate. Photolysis fo **4b** in ethanol in the presence of $CuCl_2$ and iodine with a 100-W medium pressure mercury lamp enclosed in a quartz probe which was immersed directly in the water-cooled reaction mixture gave 70% yield of **5b**. Photolysis of **4a** gave 35% of **5a** as yellow crystalline flakes. Carbethoxyphenanthro[9,10-*d*]oxazolin-2-one (**5c**) was prepared from **5a** with sodium hydride in DMF and ethyl chloroformate to give 54% of **5c**. Attempts to reduce the phenanthrene derivatives **5a–c** to the 9,10-dihydro compounds **6** under a variety of conditions failed. To overcome this difficulty we attempted an alternative approach to the preparation of **6**. Irradiation of **4b** in a degassed medium under nitrogen by the procedure recently reported by Srinivasan[5] failed to give the desired product

Table I. 9-Amino-10-hydroxy-9,10-dihydrophenanthrenes



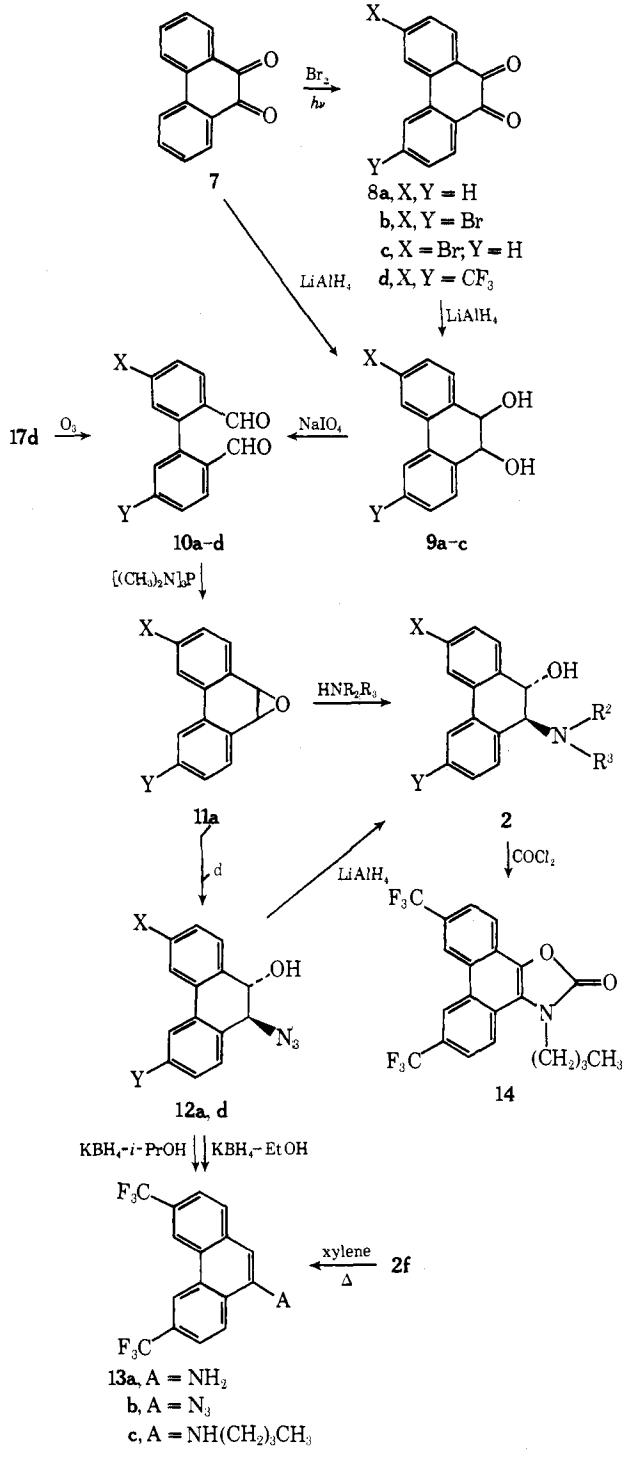
Compd	X	Y	R^2	R^3	Salt	Mp, °C	Recrystn solvent	Formula	Analyses
2a	H	H	H	$-(CH_2)_3N(Et)_2$	$\cdot 2HBr \cdot H_2O$	160–163 dec	CH_3CN	$C_{21}H_{32}Br_2N_2O_2$	C, H, N, Br
2b	H	H	H	$-(CH_2)_3CH_3$	$\cdot HCl$	204–206 dec	CH_3CN	$C_{18}H_{22}ClNO$	C, H, Cl, N, O
2c	H	H	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	$\cdot HBr$	147–149	CH_3CN–Et_2O	$C_{22}H_{30}BrNO$	C, H, N
2d	Br	Br	H	$-(CH_2)_3CH_3$	$\cdot HCl$	213–215	EtOH	$C_{18}H_{20}Br_2ClNO$	C, H, N
2e	CF_3	CF_3	H	–H	$\cdot HBr$	265 dec	CH_3CN	$C_{16}H_{12}BrF_6NO$	C, H, N
2f	CF_3	CF_3	H	$-(CH_2)_3CH_3$	$\cdot 2HBr$	223–225 dec	CH_3CN–EtOH	$C_{20}H_{20}ClF_6NO$	C, H, N
2g	CF_3	CF_3	H	$-(CH_2)_3N(Et)_2$	$\cdot 2HBr$	237–239 dec	CH_3CN–Et_2O	$C_{22}H_{28}Br_2F_6N_2O$	C, H, N[a]
2h	CF_3	CF_3	H	$-CH_2CH_2OH$	$\cdot HCl$	216–218 dec	EtOH–Et_2O	$C_{18}H_{16}ClF_6NO_2$	C, H, N
2i	CF_3	CF_3	H	$-(CH_2)_3OCH_3$	$\cdot HBr$	221–222 dec	EtOH–Et_2O	$C_{20}H_{20}BrF_6NO_2$	C, H, N
2j	CF_3	CF_3	H	$-(CH_2)_3$-c-$N(CH_2CH_2)_2O$	$\cdot 2HCl$	176–179 dec	EtOH	$C_{23}H_{26}Cl_2F_6N_2O_2$	C, H, N[b]
2k	CF_3	CF_3	H	$-(CH_2)_3OCH(CH_3)_2$	$\cdot HBr$	202–204 dec	CH_3CN–Et_2O	$C_{22}H_{24}BrF_6NO_2$	C, H, N
2l	CF_3	CF_3	H	$-(CH_2)_3NH$–(S)	$\cdot 2HCl$	264–266 dec	EtOH	$C_{25}H_{30}Cl_2F_6N_2O$	C, H, N
2m	CF_3	CF_3	H	$-CH_2CHOHCH_2OH$	$\cdot HBr$	219–221 dec	CH_3CN	$C_{19}H_{18}BrF_6NO_3$	C, H, N
2n	CF_3	CF_3	H	$-CH_2$–(N)	$\cdot HBr$	165 dec	CH_3CN–Et_2O	$C_{25}H_{32}Br_2F_6N_2O$	C, H, N[b]
2o	CF_3	CF_3	H	$-CH(CH_3)(CH_2)_3N(Et)_2$	$\cdot 2HBr$	227–229 dec	CH_3CN–Et_2O	$C_{25}H_{32}Br_2F_6N_2O$	C, H, N
12a	H	H	N	–N		134–136	EtOH–H_2O	$C_{14}H_{11}N_3O$	C, H, N
12b	CF_3	CF_3	N	–N		205–206 dec	EtOH–H_2O	$C_{18}H_9F_6N_3O$	C, H, N

[a] Calculated for hemihydrate. [b] Calculated as the hydrate.

6. Only traces of the phenanthrene derivative **5b** could be isolated.

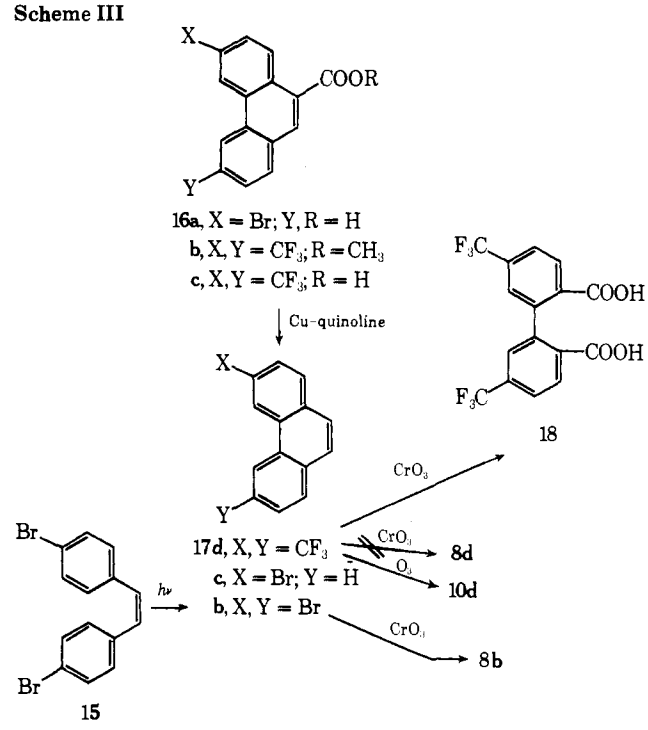
An alternative sequence which did prove to be successful involved as the key step the ring opening of the oxirane **11** with the appropriately substituted primary or sec-

Scheme II



ondary amine (Scheme II). Thus, $LiAlH_4$ reduction[6] of the phenanthrenequinones **7** and **8a,b** to the *trans*-diols **9a-c** followed by periodate oxidation[7] of **9** gave the dialdehydes **10a-c** in good yields, which on cyclization with hexamethylphosphorous triamide[8] yielded the epoxides **11a-c**. For the elaboration of a compound in the 3,6-dibromo series (*i.e.*, **2d**), advantage was taken of a literature

Scheme III



procedure[9] for the bromination of phenanthrenequinone (**7**) to 3,6-dibromophenanthrenequinone (**8b**). The reaction sequence (**7** → **8b** → **9b** → **10b** → **11b**) shown in Scheme II gave the desired epoxide **11b** in poor overall yields. An alternative approach (**15** → **17b** → **8b**) (Scheme III) to the dialdehyde **10b** involved the photocyclization of the stilbene **15** to the phenanthrene **13b**.[10,11] This route appears to be promising, subject only to a limitation in the scale of the photocyclization step. The bromination of **7** at lower temperatures gave 3-bromophenanthrenequinone (**8c**), although this reaction was found to be even more unpredictable than the dibromination of **7** to give **8b**, often giving mixtures which were difficult to separate. Alternatively, 3-bromophenanthrene-9-carboxylic acid‡ (**16a**) was decarboxylated and the resulting 3-bromophenanthrene **17c** was converted to 3-bromophenanthrenequinone (**8c**). Conversion of **8c** to 3-bromo-9,10-epoxy-9,10-dihydrophenanthrene (**11c**) was carried out as shown in Scheme II. Sufficient quantities of this epoxide were not available for further synthesis.

For the elaboration of compounds in the 3,6-bis(trifluoromethyl)phenanthrene series (**2e, f-o, 12d**, Table I), **16b** was saponified to the acid **16a** and decarboxylated to **17d** (Scheme III). Oxidation of **17d** with chromic acid unexpectedly gave the diphenic acid **18** instead of the quinone **8d**. The high yields of **18** obtained by the chromic acid oxidation of **17d** would make this method a useful preparative method for the otherwise inaccessible 3,6-disubstituted diphenic acid **18**. Conversion of the diphenic acid **18** to the desired dialdehyde **10d** through reduction of the acid chloride with lithium tri-*tert*-butoxyaluminum hydride[12] proved difficult, as did Lemieux-Johnson oxidation[13] of the phenanthrene **17d**. However, direct ozonolysis of **17d** was found to be an excellent method for the synthesis of the dialdehyde **10d**. Intramolecular cyclization gave the epoxide **11d** which was then ring opened with a variety of amines to give the amino alcohols **2f-o** (Table I). The epoxide **11d** proved to be considerably more stable to heat and less reactive than the corresponding unsubstituted epoxide **11a**. Ring opening occurred

‡ Kindly supplied by WRAIR through Dr. E. A. Steck.

readily with primary amines but not with secondary amines or with ammonia. When **11d** was treated with sodium azide, the resulting azide **12d** could be further reduced to the amine **2e** with a large excess of $LiAlH_4$ (Scheme II). Reduction of **12b** with KBH_4 in refluxing ethanol gave the phenanthrylamine **13a**, whereas reduction with KBH_4 in refluxing isopropyl alcohol gave only elimination product **13b**. The 9-butylaminophenanthrene derivative **13c** was readily prepared by the dehydration of the 9,10-dihydro-10-hydroxyphenanthrene derivative **2f** in refluxing xylene. Treatment of the amino alcohol **2f** with phosgene[14] in the presence of triethylamine gave the oxazolin-2-one derivative **14**. Attempts to reduce the 9,10 double bond in such oxazolin-2-ones proved unsuccessful in this and our previous studies involving the photocyclization of 4,5-diphenyloxazolin-2-one.

Biological Activity. All compounds reported in Table I were tested for antimalarial activity against mice infected with *P. berghei*§ or with chicks infected with *P. gallinaceum*. None of the compounds tested (Table I, plus **11d**, **8d**, **13b**, and **14**) caused any increase in mean survival time of more than 2 days in the mouse screen, with the exception of the epoxide **11d** which showed an increase in the mean survival time of 4 days at 640 mg/kg and 3.2 days at 320 mg/kg. The compounds tested were nonlethal to mice at the dosages tested (<640 mg/kg). The biological activity of **11d** is of interest since it has been reported that **11a** is capable of alkylating DNA,[16] and the amino acid formed when this epoxide is opened with L-cysteine has been shown to be incorporated into proteins.[17] Epoxides such as **11d** may therefore have some effect on plasmodial DNA by this type of interaction. Henry[18] has described a correlation between biological activity and the ability to fit to a specific site on helical DNA, as demonstrated by space-filling models, for the arylamino alcohol group of antimalarial drugs. The possibility for this type of correlation was suggested by Hahn who established that quinine[19] and a synthetic 2-phenylquinoline analog[20] bind to DNA *in vitro* by an intercalative mechanism.

The lack of antimalarial activity of structures such as **2**, which possess the essential components proposed by Henry for binding to DNA, would suggest that the structural parameters for intercalation may be more stringent than originally proposed. This leaves open for speculation the hypothesis that the phenanthrene amino alcohol antimalarials act by alkylating DNA by metabolic conversion to the 9,10-epoxide.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were recorded on a Varian T-60 spectrometer, with TMS as the internal standard. Spectral data were recorded on a Beckman IR-10 spectrometer, and uv spectra were recorded with a Beckman DB-G grating spectrophotometer. Where analyses are indicated by symbols of elements, the analytical results were within ±0.4% of the theoretical values.

3-Carbethoxy-4,5-diphenyloxazolin-2-one (4c). To 0.89 g of sodium hydride (57% in oil) was added a stirred solution of 5 g (0.021 mol) of 4,5-diphenyloxazolin-2-one (**4a**)[7] in 30 ml of DMF under nitrogen. The reaction was cooled briefly in ice, and then 2 ml of ethyl chloroformate was added dropwise at room temperature. Stirring was continued 2.5 hr, a few drops of water were added to decompose any excess hydride, and the mixture was poured into 300 ml of ice water. The precipitate was filtered off and air-dried to give 6.47 g of crude product, mp 100–104°. Recrystallization from absolute ethanol gave 4.92 g (75.4% yield) of a white crystalline product, mp 109–111°. *Anal.* ($C_{18}H_{15}O_4N$) C, H, N.

3-Methylphenanthro[9,10-*d*]oxazolin-2-one (5b). Photochemical Cyclization of 4b. The apparatus used consisted of a 2-l. brown glass jar containing a magnetic stirring bar and immersed in a bucket with a drain near the top. A 100-W mercury lamp filament connected to a transformer was placed in a quartz probe which was then immersed directly in the reaction mixture. Water circulating in the bucket maintained the temperature of the reaction mixture near 32°. During irradiation the solution in the jar was stirred and oxygen was bubbled in throughout the reaction. In a typical run, a solution of 5 g (0.02 mol) of 3-methyl-4,5-diphenyl-4-oxazolin-2-one (**4b**), 1.7 g (0.01 mol) of $CuCl_2 \cdot 2H_2O$, and 0.25 g (0.001 mol) of iodine in 1 l. of 95% ethanol was irradiated for 19 hr. The solution was then cooled in ice and the colorless crystals of **5b** were filtered off to yield 2.5 g of **5b**, mp 200–205°. Irradiation of the filtrate for another 16 hr, evaporation of the solvent to about 100 ml, and filtration yielded an additional 0.97 g of product (combined yield 69.5%). Recrystallization from ethanol gave white flakes, mp 207–209°. *Anal.* ($C_{16}H_{11}NO_2$) C, H, N.

Phenanthro[9,10-*d*]oxazolin-2-one (5a). A solution of 15.5 g (0.06 mol) of **4a**, 5.5 g of $CuCl_2 \cdot 2H_2O$, and 0.83 g of iodine in 2 l. of 95% ethanol was irradiated under nitrogen for 16 hr in the apparatus described above. Evaporation of the mother liquor gave successive crops of **5a**, total yield 6.02 g (38.8%), mp 300°. Crystallization from 95% ethanol gave **5a** as yellow crystalline flakes, mp 315°. *Anal.* ($C_{15}H_9NO_2$) C, H, N.

3-Carbethoxyphenanthro[9,10-*d*]oxazolin-2-one (5c). To 200 mg of sodium hydride (57% in oil) was added a solution of 1.2 g (5 mol) of **5c** in 20 ml of DMF under nitrogen. The reaction was cooled briefly in ice, and 0.5 ml of ethyl chloroformate was added dropwise. The reaction was stirred at room temperature for an additional 1.5 hr and was then poured into 200 ml of ice water. The precipitate was filtered off and crystallized directly from absolute ethanol to give 0.85 g (54%) of product **5c**, mp 126–129°. Recrystallization raised the melting point to 128–130°. *Anal.* ($C_{18}H_{13}NO_4$) C, H, N.

***trans*-9,10-Dihydro-9,10-dihydroxyphenanthrene (9a).** The diol **9a** was prepared by the procedure of Booth, *et al.*,[6] from **3** in 56% yield, mp 185–188° dec (lit.[6] mp 185°).

Biphenyl-2,2′-dialdehyde (6a). This compound was prepared from **5a** by the generalized procedure of Hadler and Krugger[7] in 72% yield, mp 59–61° (lit.[21] mp 62.5–63.5°).

9,10-Epoxy-9,10-dihydrophenanthrene (11a). The dialdehyde **10a** was cyclized to the epoxide **11a** by the procedure of Newman and Blum.[8] The epoxide was obtained in 84% yield, mp 109–110° (lit.[8] mp 104–105°).

***trans*-9-Butylamino-9,10-dihydro-10-hydroxyphenanthrene Hydrochloride (2b·HCl).** To 2.0 g (0.01 mol) of **11a** was added 40 ml of *n*-butylamine and the mixture was allowed to reflux with stirring until tlc showed disappearance of the epoxide **11a** (5.5 hr). The solvent was evaporated and the light yellow residue was kept at 70–90° (0.1 mm) for 2 hr. This material was then placed in an ice bath and treated with 15 ml of HCl–EtOH (2.2 g of HCl). White crystals separated on standing in the refrigerator. The solvent was again evaporated and the residue was recrystallized from 200 ml of CH_3CN containing 10 ml of Et_2O, giving the product as white needles (2.47 g, 79.0%), mp 204–206° dec (Table I).

Similarly prepared from the appropriate epoxide **11** and an amine were **2a,c,d,f–o** (Table I).

3-Bromophenanthrenequinone (9c). A. From 3-Bromo-9-phenanthrenecarboxylic Acid (16a). A mixture of 3-bromo-9-phenanthrenecarboxylic acid‡ (39.2 g, 0.13 mol), 100 ml of quinoline, and 2.0 g of copper powder was stirred under nitrogen and heated to 220–230° for 2 hr. The mixture was then cooled to 80° and poured into 700 ml of ice water containing 24 ml of concentrated H_2SO_4. The organic material was taken up in ether; the ether layer was washed with water, dried, and evaporated. The solid residue was recrystallized directly from 350 ml of 95% ethanol, giving 25.2 g (75.3%) of beige crystals of **17c**, mp 74–77° (lit.[22] mp 81–83°). The crude **17c** was oxidized directly by dissolving it almost completely in 350 ml of glacial HOAc and adding a solution of CrO_3 (39.0 g) in 200 ml of HOAc and 100 ml of water. The mixture was stirred at room temperature for 4 days. The reaction mixture was then diluted with 3 l. of water, and the product was removed by filtration, giving 16.55 g (58.8%) of orange **8c**, mp 260° dec. Recrystallization from glacial HOAc raised the melting point to 261–265° dec (lit.[9] mp 268°).

B. From Phenanthrenequinone. **8c** was also prepared by

§ Tests were carried out in five mice infected with *P. berghei* at 40, 160, and 640 mg/kg in the screening facility of Dr. L. Rane of the University of Miami.[15] Chicks were infected with *P. gallinaceum* fatal to 100% of untreated controls within 3–4 days. An increase of at least 100% survival time of treated animals was considered as active.

bromination of phenanthrenequinone by the literature procedure.[9]

3-Bromo-9,10-dihydro-9,10-dihydroxyphenanthrene (9c). A. Reduction with KBH_4. 3-Bromophenanthrenequinone (0.28 g, 1 mol) was suspended in 60 ml of absolute ethanol and treated with 0.3 g of KBH_4 in small batches. The mixture was stirred at room temperature overnight and was then cooled in ice and decomposed with 5 ml of 2 *N* HCl. The volume was reduced to about 20 ml; the residue was diluted with 100 ml of water and extracted with 150 ml of ether. The clear colorless ether layer was washed, dried, and evaporated, giving 0.25 g of crude diol, mp 194–198° dec. Recrystallization from 15 ml of *i*-PrOH gave 0.15 g (53%) of **9c**, mp 204–205° dec (free of quinone by tlc). Another recrystallization gave the analytical sample. *Anal.* ($C_{14}H_{11}BrO_2$) C, H.

B. Reduction with $LiAlH_4$. A Soxhlet thimble charged with 5.61 g (0.0195 mol) of **4c** and 250 ml of THF (dried over molecular sieves) containing $LiAlH_4$ (1.4 g, 0.0037 mol) was allowed to reflux overnight. The reaction mixture was then cooled in ice and decomposed with 10 ml of water, followed by 80 ml of 2 *N* H_2SO_4. The volume was reduced to one-third and the residue was extracted with Et_2O. The Et_2O extract was worked up in the usual way; the crude product was recrystallized from *i*-PrOH, giving a small first fraction of **8c**, followed by 1.2 g of **9c** (mp 192–184°, still containing some quinone) in the second crop, and 0.28 g of diol (mp 189–191°, also containing some quinone) in the third crop. The total yield was 26.0%.

3,6-Dibromo-9,10-dihydro-9,10-dihydroxyphenanthrene (9b). A. Reduction with KBH_4. To 0.73 g (1.9 mmol) of **8b**[9] suspended in 120 ml of absolute ethanol was added 0.6 g of KBH_4 in small batches. Most of the starting material rapidly went into solution. The yellow reaction mixture was stirred at room temperature overnight and then was decomposed with 10 ml of 2 *N* HCl while cooling in ice. About half the solvent was removed on the rotary evaporator and the remainder was diluted with 200 ml of water and extracted with 200 ml of ether. The light yellow ether extract was washed twice with water, dried over $MgSO_4$, filtered, and evaporated. The solid residue was recrystallized from 50 ml of *i*-PrOH, giving a first crop of diol **9b**, mp 194° dec, 0.35 g. Evaporation of the filtrate gave a second crop of purer material, mp 195–196° dec, 0.10 g (combined yield, 61%). *Anal.* ($C_{14}H_{10}Br_2O_2$) C, H, N.

B. Reduction with $LiAlH_4$. **8b** was reduced by the procedure described for the $LiAlH_4$ reduction of **8c** to give product **9b**, mp 192–193°, in 54% yield.

2,2′-Diformyl-5,5′-bis(dibromobiphenyl) (9b). The dialdehyde **10b** was prepared from **9b** in 54% yield by the procedure described for the preparation of **10a**, mp 108–111°. *Anal.* ($C_{14}H_8Br_2O_2$) C, H, Br.

3,6-Dibromo-9,10-epoxy-9,10-dihydrophenanthrene (11b). The dialdehyde **10b** was cyclized to the epoxide **11b** with hexamethylphosphorous triamide by the procedure described for the preparation of **10a** to give 74% of white crystalline flakes, mp 148–150°. *Anal.* ($C_{14}H_8Br_2O$) C, H, Br.

3,6-Bis(trifluoromethyl)-9-phenanthrenecarboxylic Acid (16c). The ester **16b**‡ (50.0 g) was saponified by refluxing in 100 ml of 20% NaOH and 250 ml of methanol with stirring. The yellow solution was cooled and acidified with 125 ml of concentrated HCl, and the product was filtered off, washed with a large amount of water, and dried, giving 49.7 g (100%) of a white crystalline solid, mp 264–265°.

3,6-Bis(trifluoromethyl)phenanthrene (17d). A mixture of 3,6-bis(trifluoromethyl)-9-phenanthrenecarboxylic acid (**16b**, 25.0 g), 50 ml of quinoline, and 1.5 g of copper powder was allowed to reflux with stirring under nitrogen for 2 hr. The cooled mixture was poured into 400 ml of ice water containing 80 ml of concentrated HCl, and the beige precipitate was removed by filtration and recrystallized from ethanol, giving 18.3 g (83%) of product, mp 135–137°.

5,5′-Bis(trifluoromethyl)diphenic Acid (18). To 2.5 g (8 mmol) of **17d** dissolved in glacial HOAc was added a solution of 6.4 g of CrO_3 in 20 ml of water and 40 ml of glacial HOAc. The mixture was stirred at room temperature for 4 days and then heated on the steam bath for 5 hr. The product was removed by filtration, giving 2.30 g (76.5%) of **18** as a whitish powder, mp 226–235°. Recrystallization from aqueous ethanol gave white crystalline flakes, mp 232–234°. *Anal.* ($C_{16}H_8F_6O_4$) C, H, F.

2,2′-Diformyl-5,5′-bis(trifluoromethyl)biphenyl (10d). The reaction was carried out with a Welsback T10 ozonator by the procedure described for the preparation of diphenaldehyde.[21] Thus **17d** (8.0 g, 0.025 mol) was dissolved in 600 ml of warm anhydrous CH_3OH and was then cooled rapidly in a Dry Ice–acetone bath to give a fine suspension. Ozone was then passed in at a flow rate of 0.02 ft^3/min and a concentration of 70–80 mg/l. while the internal temperature was maintained at −5 to −15°. After 6.5 hr tlc showed disappearance of the starting material. The intermediate hydroperoxide was reduced by simultaneously adding 14 g of sodium iodide and 14 ml of glacial acetic acid and the reaction mixture was then stirred at room temperature for 1 hr. The liberated iodine was reduced with 150 ml of 10% $Na_2S_2O_3$. The solvent was evaporated until the organic material began to separate. The product was obtained as a white solid after standing in the refrigerator overnight, mp 67–71°, 8.04 g (91%). A 2,4-DNP derivative was prepared, mp 275.5–276.5° dec. Recrystallization from aqueous ethanol did not improve the melting point. The aldehyde protons were observed as a sharp singlet at δ 9.8 in the nmr spectrum (no impurities were shown by the nmr). *Anal.* ($C_{16}H_8F_6O_2$) C, H.

9,10-Epoxy-9,10-dihydro-3,6-bis(trifluoromethyl)phenanthrene (11d). A mixture of **10d** (6.45 g, 0.019 mol) and hexamethylphosphorous triamide (3.05 g, 0.02 mol) in 200 ml of benzene was allowed to reflux with stirring for 30 min. The solvent was evaporated to dryness and the crude material was washed with 15 ml of cold cyclohexane to remove excess phosphorus compounds. The residue was recrystallized directly from cyclohexane, giving a first crop of white product (4.01 g, 65%), mp 185–187°. Evaporation of the solvent gave a small second crop (0.37 g, 6%), mp 187–189° (the product changes crystalline form near 155°). The uv spectrum showed λ_{max} (EtOH) 273 mμ (biphenyl). The ir spectrum showed strong epoxide bands at 905, 825, and 750 cm^{-1}. The protons at the 9,10 positions were observed as a sharp singlet at δ 4.5 in the nmr spectrum. *Anal.* ($C_{16}H_8F_6O$) C, H.

***trans*-9-Azido-9,10-dihydro-10-hydroxy-3,6-bis(trifluoromethyl)phenanthrene (12d).** To 4.3 g (0.013 mol) of **11d** suspended in 125 ml of 95% ethanol, a solution of sodium azide (0.94 g, 0.014 mol) and ammonium chloride (0.77 g, 0.014 mol) in 25 ml of water was added. The mixture was allowed to reflux with stirring for 2 hr. The product precipitated on cooling, giving 4.40 g (90.5%) of white needles, mp 205–206° dec. Recrystallization from aqueous ethanol gave the analytical sample. *Anal.* ($C_{16}H_9F_6N_3O$) C, H, N.

Similarly prepared from **11a** in 90% yield was ***trans*-9-azido-9,10-dihydro-10-hydroxyphenanthrene (12a)**, mp 134–136° (EtOH). *Anal.* ($C_{14}H_{11}N_3O$) C, H, N.

9-Amino-3,6-bis(trifluoromethyl)phenanthrene (13a). A mixture of **12d** (0.24 g, 0.64 mmol) and 0.1 g of KBH_4 in 50 ml of absolute EtOH was allowed to reflux for 1 hr, the solvent was evaporated, and the whitish residue was partitioned between ether and water. The ether layer was washed with water, dried, and evaporated to give 0.15 g (72%) of **13a**. Recrystallization from 95% ethanol gave an off-white solid, mp 191–193°. *Anal.* ($C_{16}H_9F_6N$) C, H, N.

9-Azido-3,6-bis(trifluoromethyl)phenanthrene (13b). A mixture of 10 g of **12d** (2.7 mmol) and 0.34 g (6.2 mmol) of KBH_4 in 50 ml of *i*-PrOH was allowed to reflux with stirring for 2 hr. An orange color developed during the first half hour. After standing at room temperature overnight, the solvent was evaporated, and the residue was taken up in 100 ml of CH_2Cl_2. The organic layer was washed with water, dried, and evaporated, giving 0.95 g of crude orange product decomposing above 170°. Recrystallization from 95% EtOH gave 0.57 g (60%) of crystalline flakes, mp 181–182° dec. *Anal.* ($C_{16}H_7F_6N_3$) C, H, N.

9-*n*-Butylamino-3,6-bis(trifluoromethyl)phenanthrene (13c). A mixture of 1.5 g (3.7 mmol) of **2f** and 0.46 g of benzoic acid in 45 ml of xylene was allowed to reflux overnight with a Dean-Stark trap. Evaporation of the xylene gave an oil which solidified on cooling to give 1.1 g (79%) of crude **13c** which, after washing and recrystallization from aqueous ethanol, gave a light yellow solid, mp 139–141°. *Anal.* ($C_{20}H_{17}F_6N$) C, H, N.

***trans*-9-Amino-9,10-dihydro-10-hydroxy-3,6-bis(trifluoromethyl)phenanthrene Hydrobromide (2e).** To 1.1 g (3 mmol) of **12d** was added a stirred suspension of 0.5 g of $LiAlH_4$ in 200 ml of anhydrous ether. The addition was slightly exothermic. The mixture was stirred for 2 hr at room temperature, then cooled in ice, and hydrolyzed with water. The ether layer was washed with water, dried, and acidified with HBr–EtOH, giving a first crop of 0.3 g of white product, mp 265° dec. The filtrate was evaporated and the residue was crystallized from CH_3CN to give 0.5 g of white product in two crops, mp 265° dec (combined yield, 63.5%). *Anal.* ($C_{16}H_{12}BrF_6NO$) C, H, N.

3-(*n*-Butylamino)-6,9-bis(trifluoromethyl)phenanthro[9, 10]-oxazolin-2-one (14). A solution of 2.1 g of **2f** and 10 ml of triethylamine in 100 ml of benzene was cooled in an ice bath while pro-

tected with a drying tube. A solution of phosgene (55 ml, 12.5% in benzene) was then added with vigorous stirring. The reaction was cooled for an additional 10 min and was then kept at room temperature for 1 hr. The reaction mixture was cooled again, treated with 100-ml portions of 1 *N* HCl until free of amine, and then rinsed successively with 8% $NaHCO_3$ and water, dried, and evaporated, giving a thick oil which solidified in methanol. Recrystallization from 95% ethanol to give a crystalline product, 1.08 g (46.5%), mp 110–113°. *Anal.* ($C_{21}H_{15}F_6NO_2 \cdot H_2O$) C, H, N.

Acknowledgments. We wish to thank Drs. E. A. Steck and T. R. Sweeney for their counsel and for making available to us a generous supply of a number of key starting materials. The skillful technical assistance of Ms. E. Hayes, G. Millar, and Mr. W. Smolnycki in the preparation of several intermediates is gratefully acknowledged. The authors also wish to thank Dr. C. B. Boyce for valuable suggestions and discussions of the photochemical approaches.

References

(1) E. A. Steck, "The Chemotherapy of Protozoan Diseases," Vol. III, Walter Reed Army Institute of Research, 1972, p 23.63, and references cited therein.
(2) (a) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 627 (1946); (b) E. A. Nodiff, E. Tanabe, C. Seyfried, S. Matsuura, Y. Kondo, E. H. Chen, and M. P. Tyagi, *J. Med. Chem.*, 14, 921 (1971).
(3) A. S. Dey and J. L. Neumeyer, Second Northeast Regional Meeting of the American Chemical Society, Providence, R. I., Oct 1970, Abstract No. 122.
(4) R. Gompper, *Ber.*, **89**, 1748 (1956).
(5) R. Srinivasan and J. N. C. Hsu, *J. Amer. Chem. Soc.*, **93**, 2816 (1971).
(6) J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, 1188 (1950).
(7) H. I. Hadler and A. C. Krugger, *J. Org. Chem.*, **25**, 1896 (1960).
(8) M. S. Newman and S. Blum, *J. Amer. Chem. Soc.*, **86**, 5598 (1964).
(9) M. V. Bhatt, *Tetrahedron*, **20**, 803 (1963).
(10) J. A. Stanfield and L. B. Reynolds, Jr., *J. Amer. Chem. Soc.*, **74**, 2878 (1952).
(11) F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964).
(12) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley, New York, N. Y., 1969, p 251.
(13) Reference 12, Vol. 1, p 812.
(14) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967), and references cited therein.
(15) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(16) P. L. Grover and P. Sims, *Biochem. Pharmacol.*, **19**, 2251 (1970).
(17) D. M. Jerina, H. Ziffer, and J. W. Daly, *J. Amer. Chem. Soc.*, **92**, 1056 (1970).
(18) D. W. Henry, Abstracts, 13th Medicinal Chemistry Symposium, Iowa City, Iowa, June 1972, p 41.
(19) R. Estensen, A. Krey, and F. Hahn, *Mol. Pharmacol.*, **5**, 532 (1969).
(20) F. Hahn and C. Fean, *Antimicrob. Ag. Chemother.*, **1969**, 63 (1970).
(21) P. S. Bailey and R. E. Erickson, "Organic Syntheses," Collect. Vol. V, Wiley, New York, N. Y., 1973, p 489.
(22) C. S. Wood and F. B. Mallory, *J. Org. Chem.*, **29**, 3373 (1964).

Structure–Activity Relationships in Psychotomimetic Phenylalkylamines

F. A. B. Aldous, B. C. Barrass, K. Brewster, D. A. Buxton, D. M. Green, R. M. Pinder,*,† P. Rich, M. Skeels, and K. J. Tutt

Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, England. *Received March 19, 1974*

A study has been made of the relationship between the structure of phenylalkylamines and potential correlates of their psychotomimetic activity. Optimum activity is associated with (a) an isopropylamine side chain, with a *R*-(−) configuration at the carbon atom α to the amino group, and (b) 2,5-dimethoxy substitution, together with an alkyl or halo group at position 4 that is probably limited in bulk to *n*-propyl or bromo. The activity of compounds in producing hyperthermia in rabbits provides good quantitative correlation with reported psychotomimetic activities in man.

Phenylalkylamines, and in particular phenylisopropylamines or amphetamines, are one of the few types of psychotomimetic compound for which extensive structure–activity relationships (SAR) are available.[1] Many of them have been tested in man[2] but, while a variety of procedures has been used such as disruption of conditioned avoidance responses (CAR) in rats[3,4] and inhibition of swim-maze performance in mice,[5] there is no wholly satisfactory animal testing procedure which allows quantitative comparison of relative potencies. The latter is especially important where enantiomeric potency ratios are concerned, though it is claimed that clinical observation in man[6] or CAR in rats[7] provides sufficient delineation of the psychotomimetic activities of the *R* and *S* enantiomers of the 2,5-dimethoxy-4-methyl derivative of amphetamine (DOM, STP). Furthermore, a correlation apparently exists between the smooth muscle stimulating activity of phenylisopropylamines and their known psychotomimetic activity in man.[8] We report SAR in psychotomimetic phenylalkylamines, using pharmacological methods which we believe provide a more reliable and accurate measure of relative potencies. Our study includes the effects upon activity of both ring substitution and variation in the alkylamine side chain.

Chemistry. Phenylisopropylamines containing different ring substituents were prepared by the classical route of Knoevenagel condensation between the appropriate benzaldehyde and nitroethane, followed by $LiAlH_4$ reduction.[5] Their homologs, the 3-amino-1-phenylbutanes, were obtained by oximation and reduction of the corresponding 1-phenylbutan-3-ones. Both cis and trans isomers of various 2-phenylcyclopropylamines were derived from the same synthetic sequence, Curtius transformation of the mixed ester from reaction of the appropriate styrene with ethyl diazoacetate;[9] solely trans isomers were also obtained from the trans ester resulting from reaction between *trans*-cinnamates and dimethylsulfoxonium methylide.[10] Other side-chain variations based on the 2,5-dimethoxy-4-methylphenyl skeleton involved successive alkyla-

*Address correspondence to this author at the Australasian Drug Information Services Pty Ltd., Takapuna North, Auckland 9, New Zealand.

†This paper is dedicated to my former mentor and colleague, Alfred Burger.