H_2O was added to ppt 4.4 g of 11. Other compds in Table II were obtained by this method.

2-(α-Methyl-α-hydroxybenzyl)benzoxazole (9).—A soln of **10** (2.65 g) in anhyd Et_2O (50 ml) was dropped slowly into a soln of MeMgBr (1.36 g) in 50 ml of anhyd Et_2O with stirring and cooling. After 6 hr at room temp 30 ml of H_2O and 1 ml of concd HCl were added, and the org layer sepd, was washed with H_2O, and dried ($MgSO_4$). After evapn of the solvent, 1.6 g of white solid (**9**) was collected. 2-(α-Methyl-α-hydroxybenzyl)-5-chlorobenzoxazole (**10**) was obtained in the same way (Table I).

Acknowledgments.—The authors wish to thank J. Sorge and K. Young for carrying out the antiviral experiments. The financial assistance of the SRI-Institute Research and Development Program is acknowledged for the antiviral studies.

3- and 4-Carbazole Dialkylaminocarbinols as Potential Antimalarial Agents

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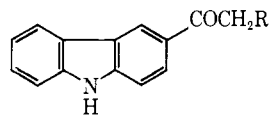
The important role of quinolinemethanol compounds in malaria chemotherapy has prompted the investigation of other heteroaryl carbinols for antimalarial activity. Accordingly we have synthesized 3- and 4-(α-hydroxy-β-dibutylaminoethyl)carbazole and tested the compounds for their antimalarial action against *Plasmodium berghi* in mice. Unfortunately neither compound showed significant activity in this test system, as shown in Table I.

TABLE I

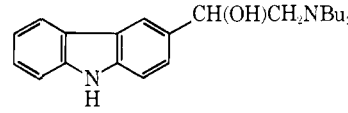
	Antimalarial bioassay result[a]			
	Dose, mg/kg			
Compd	40	160	320	640
4	0.3	0.3		0.5
8	0.2	0.4	0.8	

[a] Increase in survival time (days) of treated mice beyond that of untreated controls after single sc dosages (3 days postinfection). Average survival time of untreated controls was 7.0 ± 0.5 days. The infecting organism was *P. berghei*.

The synthesis of the 3 isomer began with 3-acetylcarbazole **1** followed by bromination and reaction of the bromo ketone **2** with Bu_2NH. Reduction of the amino ketone **3** with $NaBH_4$ readily afforded the amino alcohol **4**. The acid chloride of carbazole-4-carboxylic acid **5** was treated with CH_2N_2 to give the chloromethyl ketone **6**. A similar displacement with Bu_2NH and reduction yielded **8**.



1, R = H
2, R = Br
3, R = NBu_2



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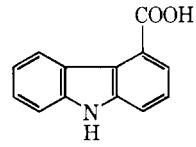

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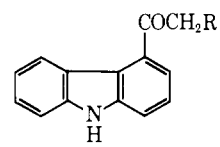
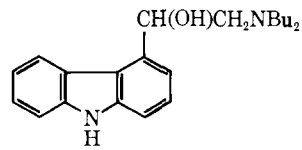


6, R = Cl
7, R = NBu_2



8

3-Dibutylaminoacetylcarbazole (3).—A mixt of 7.4 g of **2**, 40 ml of n-Bu_2NH, and 150 ml of MeOH was refluxed 3 hr and evapd *in vacuo*, finally at 1 mm. The residue was treated with 200 ml of H_2O, acidified to pH 1–2 with concd HCl, and washed with 200 ml of EtOAc. The acid phase containing much insol, oily HCl salt of the product was alkalized with 10% NaOH to pH 10–11. The oily ppt was extd into 200 ml of Et_2O which was washed with H_2O, dried ($MgSO_4$), and evapd to leave 4.4 g of syrup. After two pentane washes the syrup was dried at 1 mm to leave 4.0 g which solidified. A portion was recrystd for anal., mp 106–112° (pentane–C_6H_6). *Anal.* ($C_{22}H_{28}N_2O$): C, calcd 78.5; found 78.0.

3-(α-Hydroxy-β-di-n-butylamino)ethylcarbazole (4).—A mixt of 4.0 g of **3**, 1.5 g of $NaBH_4$, and 150 ml of EtOH was warmed into soln and stirred for 20 hr at room temp. The solvent was evapd *in vacuo* and the residue was partitioned between Et_2O and H_2O. The Et_2O was dried ($MgSO_4$) and evapd to leave 2.7 g of gum, which was extd with three 90-ml portions of boiling pentane. The ext was gassed with HCl. The hygroscopic salt was collected and triturated with 10 ml of Me_2CO and the white cryst were collected (1.10 g, 25%), mp 165–168°. *Anal.* ($C_{22}H_{30}N_2O \cdot HCl$).

4-Chloroacetylcarbazole (6).—The mixt of tetrahydrocarbazole-5- and -7-carboxylic acids[2] was readily sepd as the Me esters by silica gel chromatography. Dehydrogenation of the 5 isomer followed by saponification afforded 4-carboxycarbazole (**4**).[3] A soln of the acid chloride (from 3.16 g of acid and 1.1 ml of $SOCl_2$ in 50 ml of C_6H_6) in 40 ml of CH_2Cl_2 was added dropwise to 45 mmoles of CH_2N_2 in 150 ml of Et_2O at 0–5°. After 1 hr at 0–5° the soln was gassed with HCl for 20 min and evapd *in vacuo* (2.52 g). Chromatography on silica gel gave 2.07 g (57%), mp 158–160.5°. *Anal.* ($C_{14}H_{10}ClNO$).

4-Dibutylaminoacetylcarbazole (7).—A mixt of 1.47 g of **6** and 20 ml of Bu_2NH was stirred at 35–40° for 15 hr. A work-up similar to that for the 3 isomer gave an orange syrup (1.0 g, 49%), which slowly crystd; recrystd, mp 196–204° (EtOH). Elemental anal. and bands at 3.9–4.2 μ in the ir indicated a carbonate salt. *Anal.* ($C_{22}H_{28}N_2O)_2 \cdot H_2CO_3$.

4-(α-Hydroxy-β-di-n-butylamino)ethylcarbazole Picrate (8).—The ketone **7** was reduced with $NaBH_4$ in EtOH as above to yield a yellow syrup (36%). The picrate, mp 174–179°, was obtained from EtOH–H_2O. *Anal.* ($C_{28}H_{33}N_5O_8$).

Experimental Section

Compounds followed by empirical formulas only were analyzed for C, H, N with values within ±0.4% of theoretical.

3-Bromoacetylcarbazole (2).—A mixt of 10.7 g (0.029 mole) of $PhMe_3N^+ \cdot 3Br^-$, 6.0 g (0.029 mole) of 3-acetylcarbazole[1] (**1**), and 100 ml of THF was stirred at room temp for 5 hr, then evapd *in vacuo*. The residue was thoroughly washed with H_2O and Et_2O to yield 7.1 g (86%); mp 158–159°; anal. sample, mp 160–162° (C_6H_6). *Anal.* ($C_{14}H_{10}BrNO$): Br.

(1) E. Meizner, *J. Amer. Chem. Soc.*, **57**, 2327 (1935).

(2) W. M. Collar and S. G. Plant, *J. Chem. Soc.*, 808 (1926).

(3) P. H. Carter, S. G. Plant, and M. Tomlinson, *ibid.*, 2210 (1957).

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Antimalarial Agents. 7. Compounds Related to 4,4′-Bis(aminophenyl) Sulfone[1]

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4,4′-Bis(acetamidophenyl) sulfone (I) and its lower homolog (II) are highly active[2] against *Plasmodium berghei* in mice. Since they are less toxic[2] than 4,4′-bis(aminophenyl) sulfone [4,4′-diamino(diphenyl sulfone), DDS, III], it was of interest to investigate the antimalarial activity of some other DDS-related compounds in which one or both NH_2 groups of III were replaced by NSO, NHOH, $NHNH_2$, NO_2, etc. Our study also included structures containing the moieties S, SO, SO_2CH_2, and SO_2S instead of the SO_2 bridge, as well as a pyridine analog of DDS.

The *N*-sulfinylamines XII [mp 149–152°, from PhH, 62% yield, *Anal.* ($C_{12}H_8N_2O_3S_2$): C, H, N] and XXIII [mp 126–128° from 1:1 petr ether–PhMe, 86% yield, *Anal.* ($C_{12}H_9NS_2O_3$): N] were synthesized from the corresponding amines by the method for 4,4′-bis(sulfinylaminophenyl) sulfone (IV) described in the Experimental Section, which includes the preparation of the remaining new compounds.

The testing[1c] was carried out by a method described previously[3] and the detailed data are listed in Tables I–IV.

None of the compounds reported here was more active than I in the mice test. Replacement of one of the NH_2 groups of DDS (III) with H or Cl resulted in total loss of antiplasmodial activity (XXII–XXVII) but not of toxicity (XXII). The oxidation of one NH_2 to NO_2, however, did not render the resulting structures completely inactive provided that the second NH_2 of III was not disubstituted as in the inactive VII, XIV, XVII, and XX. The activity of the sydnones XVIII and XIX, and of the *N*-sulfinyl structure XII, in which the second NH_2 is disubstituted, can be explained by the relative ease of hydrolysis of the sydnonyl and *N*-sulfinyl moieties to $NHNH_2$ (XIII) and NH_2 (XI), respectively. The relative activity of the pairs I–VIII, I–IX, V–XI, and VIII–IX leads to the speculation that a possible metabolism of the NO_2 group to NH_2, rather than the reverse, could be part of the mode of action of

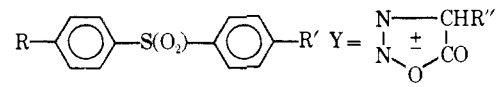
(1) (a) Part 6, *J. Med. Chem.*, **13**, 1002 (1970); (b) this study was supported by U. S. Army Medical Research and Development Command. This is Contribution No. 889 from the Army Research Program on Malaria; (c) the compounds were tested by Dr. L. Rane of the University of Miami, Florida; (d) analyses are indicated by symbols of the elements, since analytical results obtained for these elements were within ±0.4% of the theoretical values.

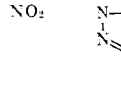
(2) Test data supplied by Dr. Bing Poon of Walter Reed Army Institute for Research.

(3) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

TABLE I

ACTIVITY OF

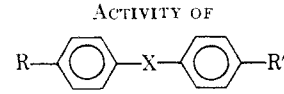


No.	Structure R	Structure R′	% cures or (CIST[h]) at mg/kg 40	160	640
I[a]	R′	NHAc	20	100	100
II[a]	R′	NHCOH	20	100	60[m]
III[a]	R′	NH_2	(8.0)	40	20[m]
IV	R′	NSO	(11.8)	20	*m*
V[b]	NH_2	NHOH	20	100	*m*
VI[c]	NH_2	$NHNH_2$	(10.4)	20	40[m]
VII[c]	NH_2	$N(NO)CH_2COX$[n]	(0.2)	(0.2)	(0.6)
VIII[d]	NO_2	NHAc	(8.3)	60	80
IX[b]	NHOH	NHAc	60[i]	60	100
X[e]	NH_2	NHAc	40	60[k]	40[m]
XI[f]	NO_2	NH_2	(8.2)	40	100
XII	NO_2	NSO	(6.6)	40	60[m]
XIII[c]	NO_2	$NHNH_2$	(13.9)	100[l]	*m*
XIV[c]	NO_2	$NAcCH_2CO_2Et$	(0.2)	(0.2)	(0.2)
XV[c]	NO_2	$NHCH_2CO_2Et$	(3.1)	(7.7)	80
XVI[c]	NO_2	$NHCH_2CO_2H$	(2.0)	(7.3)	40
XVII[c]	NO_2	$N(NO)CH_2CO_2H$	(0.2)	(0.2)	*m*
XVIII[c]	NO_2	Y (R″ = H)	(3.5)	20	60
XIX[c]	NO_2	Y(R″ = Br)	(5.3)	40	80
XX	NO_2	$N(Ac)CH(Me)CO_2Et$	(0.5)	(0.7)	(1.9)
XXI	NO_2	$NHCH(Me)CO_2Et$	(4.7)	(9.7)	80
XXII[g]	H	NH_2	(1.3)[j]	(4.1)	(4.4)[m]
XXIII	H	NSO	(0.8)	(1.2)	(1.8)
XXIV	H	$NHCH_2CO_2Et$	(0.9)	(0.9)	(1.1)
XXV	H	Y(R″ = H)	(0.5)	(0.7)	(1.9)
XXVI	Cl	$N(NO)CH_2CO_2H$	(1.5)	(0.7)	*m*
XXVII	Cl	Y(R″ = H)	(0.7)	(1.5)	(3.7)
XXVIII[c]	NO_2		(0.7)	(0.7)	(0.9)

[a] Test data supplied by Dr. Bing Poon of Walter Reed Army Institute for Research. [b] S. Owari, *Yakugaku Zasshi*, **71**, 246 (1951). [c] G. H. Singhal and I. C. Popoff, *J. Heterocycl. Chem.*, **5**, 217 (1968). [d] C. W. Ferry, J. S. Buck, and R. Baltzly, "Organic Syntheses," Collected Vol. 3, Wiley, New York, N. Y., 1955, p 239. [e] G. W. Raizis, L. W. Clemence, M. Severac, and J. C. Moetsch, *J. Amer. Chem. Soc.*, **61**, 2763 (1939). [f] Yo. O. Gabel and F. L. Grinberg, *Zh. Prikl Khim. (Leningrad)*, **12**, 1481 (1939); *Chem. Abstr.*, **34**, 6244[4] (1940). [g] W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2406 (1923). [h] Change in survival time, *i.e.*, mean survival time of treated mice minus the mean survival time of the control. [i] CIST of 10.3 at 20 mg/kg. [j] CIST of 1.9 and 1.7 at 80 and 20 mg per kg, respectively. [k] 80% cures at 320 mg/kg. [l] 20% cures at 320 mg/kg. [m] See Table IV for toxicity data. [n] X = $NHCH_2Ph$.

TABLE II

ACTIVITY OF



No.	Structure R	Structure R′	X	CIST[h] or (% cures) at mg/kg 40	160	640
XXIX[a]	NO_2	$NHCH_2CO_2Et$	S	5.7	7.7	11.1
XXX[a]	NO_2	$N(Ac)CH_2CO_2Et$	S	0.2	0.4	0.8
XXXI[b]	R′	NH_2	SO	4.1	8.7	*i*
XXXII[c]	R′	NHAc	SO	3.8	6.8	(40)[j]
XXXIII[d]	R′	NO_2	SO	3.3	8.5	(60)
XXXIV[e]	R′	NH_2	SO_2S	0.5	0.7	2.3
XXXV[f]	R′	NHAc	SO_2S	0.1	0.1	0.3
XXXVI[g]	R′	NH_2	SO_2CH_2	0.1	0.1	0.3
XXXVII	R′	NHAc	SO_2CH_2	0.1	0.1	0.3
XXXVIII	NO_2	NH_2	SO_2CH_2	1.4	1.4	1.8
XXXIX[g]	NO_2	NHAc	SO_2CH_2	1.0	1.2	1.2

[a] See footnote *c* of Table I. [b] M. Gazdar and S. Smiles, *J. Chem. Soc.*, 1833 (1908). [c] W. Braun, German Patent 964,593 (1957); *Chem. Abstr.*, **53**, P12240*h* (1959). [d] H. H. Szmant and J. J. McIntoch, *J. Amer. Chem. Soc.*, **73**, 4356 (1951). [e] B. J. Boldyrev and L. M. Khovalko, *Zh. Obsch. Khim.*, **31**, 3483 (1961); *Chem. Abstr.*, **57**, 9719*e* (1962). [f] C. Bere and S. Smiles, *J. Chem. Soc.*, 2359 (1924). [g] B. R. Baker and M. V. Querry, *J. Org. Chem.*, **15**, 413 (1950); [h] See footnote *h* of Table I. [i] See Table IV for toxicity data. [j] 20% cures at 320 mg/kg.