IIIl$_1$, 89145-08-4; IIIl$_2$, 89144-82-1; IIIl$_3$, 89144-89-8; IIIj$_1$, 89145-09-5; IIIj$_2$, 89144-83-2; IIIj$_3$, 89144-90-1; IIIk$_1$, 89145-10-8; IIIk$_2$, 89144-84-3; IIIk$_3$, 89144-91-2; IIIl$_1$, 89144-78-5; IIIl$_2$, 89144-85-4; IIIl$_3$, 89144-92-3; IIIm$_3$, 89144-93-4; IIIn$_3$, 89144-94-5; **IVa**, 30693-34-6; **IVb**, 89144-76-3; **IVc**, 89144-77-4; C_6H_5CHO, 100-52-7; *p*-ClC_6H_4CHO, 104-88-1; *p*-$CH_3OC_6H_4CHO$, 123-11-5; C_4H_3SCHO, 30583-13-2; C_4H_4NCHO, 89145-04-0; C_5H_4NCHO, 26445-06-7; C_6H_5COMe, 98-86-2; *p*-ClC_6H_4COMe, 99-91-2; *p*-$CH_3OC_6H_4COMe$, 100-06-1; C_4H_3SCOMe, 39709-34-7; C_4H_3OCOMe, 25154-45-4; NH_2NH_2, 302-01-2; $NHPhNH_2$, 100-63-0; $NHMeNH_2$, 60-34-4.

Literature Cited

(1) Duffin, G. F.; Kendall, J. D. *J. Chem. Soc.* **1954**, 408.
(2) Wiley, R. H.; Jarboe, C. H.; Hayes, F. N.; Hansbury, E.; Nielson, T.; Callahan, P. X.; Sellars, M. C. *J. Org. Chem.* **1955**, *23*, 732.
(3) Laude, B.; Khanh, Le Quoc. *Spectrochim. Acta, Part A* **1975**, *31*, 1121.
(4) Stamper, M.; Aycock, B. F. *J. Am. Chem. Soc.* **1954**, *76*, 2786.
(5) Katrib, A.; El-Rayyes, N. R.; Al-Kharafi, F. M. *J. Electron Spectrosc. Relat. Phenom.* **1983**, *31*, 317.
(6) (a) Bellamy, L. J. "The Infrared Spectra of Complex Molecules"; Chapman and Hall: London, 1975; p 289. (b) *Ibid.*, p 241.
(7) Oluwadiya, J. O. *J. Heterocycl. Chem.* **1981**, *1*,, 1293.
(8) Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802.
(9) Evands, N. A.; Whelan, D. J.; Johns, R. B. *Tetrahedron* **1965**, *21*, 3351.
(10) El-Rayyes, N. R.; Al-Hajjar, F. H. *J. Heterocycl. Chem.* **1977**, *14*, 367.
(11) Ferres, H.; Hamdam, M. S.; Jackson, W. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 936.
(12) Elguero, J.; Marzin, C. *Bull. Soc. Chim. Fr.* **1973**, 3401.
(13) Beech, S. G.; Turnbull, J. H.; Wilson, W. *J. Chem. Soc.* **1952**, 4686.

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Syntheses and Antibacterial Activity of Some New *N*-(3-Methyl-2-quinoxaloyl) Amino Alcohols and Amine 1,4-Dioxides

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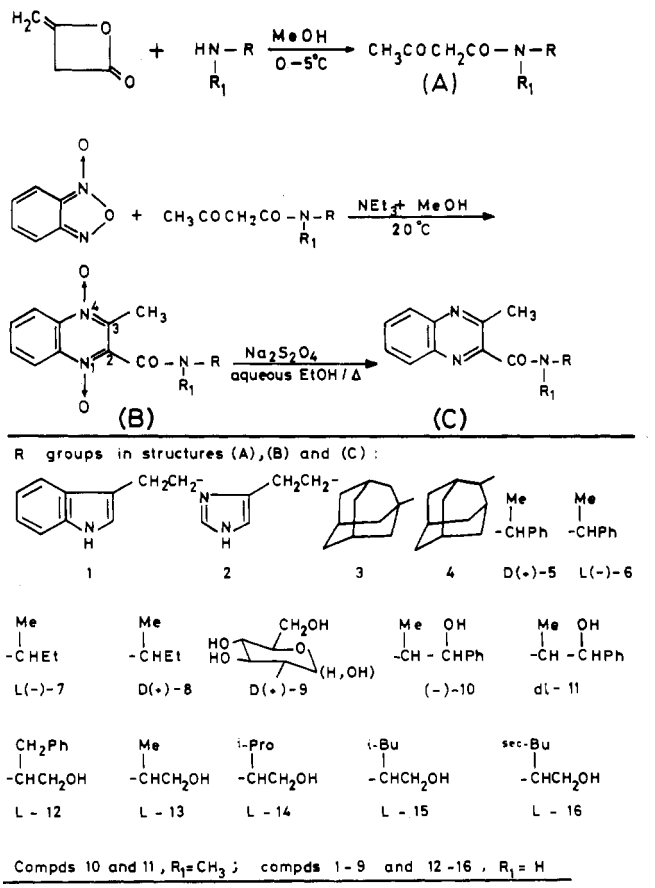
The syntheses and in vitro and in vivo antibacterial activities of a series of *N*-(3-methyl-2-quinoxaloyl) amino alcohols and amine 1,4-dioxides, and their deoxygenated analogues, are described. The quinoxaline 1,4-dioxide derivative of the naturally occurring (-)-ephedrine was found to be the most potent antibacterial agent of the series. The presence of a hydroxy group and a tertiary amide appears to be associated with enhancement of the antibacterial action.

The chemistry and biological activity of heterocyclic *N*-oxides have received considerable attention for the past two decades (*1*, *2*). In particular, various biological activities of several substituted quinoxaline 1,4-dioxides have been described in recent patent reports (*3*-*7*). These 1,4-dioxides are conveniently prepared via interaction of benzofuroxan (BFO) with enamines or enolate anions, "the Beirut reaction" (*8*).

As an extension to previous studies on quinoxaline amino acid *N*-oxides (*9*, *10*), we now report on the syntheses and in vitro and in vivo antibacterial activity of new quinoxaline 1,4-dioxide derivatives of some biologically interesting amino compounds.

The *N*-acetoacetyl precursors (A), quinoxaline 1,4-dioxides (B), and quinoxalines (C) are synthesized as depicted in Scheme I; their physical data are presented in Table I.

Scheme I



Biological Activity

The quinoxaline 1,4-dioxides (B) were tested for antibacterial activity. The results obtained showed that the quinoxaline 1,4-dioxide derivative of (-)-ephedrine (compound ***10B***) is the most effective bacteriostatic agent of the series. This compound exhibited in vitro bacteriostatic activity against *Mycobacterium tuberculosis*, *Escherichia coli*, and *Pseudomonus aeruginosa* at minimal inhibitory concentrations (MIC) of 1, 2, and 78 μg/mL, respectively. In vivo (mice) experiments indicated that ***10B*** was also active against *E. coli* (CD 50 = 35 mg/kg, po) but was inactive against *P. aeruginosa* (a species known to develop R-plasmid-mediated resistance to the penicillin derivatives (*11*)). Compound ***10B*** also exhibited a selective activity against *Staphylococcus aureus*, and *Proteus vulgaria*

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Table I. Physical Properties of New Compounds (1-16)[a]

	N-acetoacetyl compds (A)			quinoxaline 1,4-dioxides (B)			quinoxalines (C)		
no.	mp,[b] °C (solvent)	$[\alpha]^{20}_D$,[c] deg	formula[d]	mp,[b] °C (solvent)	$[\alpha]^{20}_D$,[c] deg	formula[d]	mp,[b] °C (solvent)	$[\alpha]^{20}_D$,[c] deg	formula[d]
1	78 (H + P)		$C_{14}H_{16}N_2O_2$	214 (M)		$C_{20}H_{18}N_4O_3$	182 (M)		$C_{20}H_{18}N_4O$
2	102 (M)		$C_9H_{13}N_3O_2$	185 dec (M)		$C_{15}H_{15}N_5O_3$	206 dec (M)		$C_{15}H_{15}N_5O$
3	80 (P)		$C_{14}H_{21}NO_2$	243 (M)		$C_{22}H_{23}N_3O_3$	168 (M + W)		$C_{20}H_{23}N_3O$
4	97 (P)		$C_{14}H_{21}NO_2$	229 (E)		$C_{20}H_{23}N_3O_3$	135 (M + W)		$C_{20}H_{23}N_3O$
5			g	206 (H + P)	−28.8	$C_{18}H_{17}N_3O_3$	96 (M + W)	−168.3	$C_{18}H_{17}N_3O$
6			g	208 (H + P)	+29.0	$C_{18}H_{17}N_3O_3$	95 (M + W)	+169.7	$C_{18}H_{17}N_3O$
7			g	193 (H + P)	+15.8	$C_{14}H_{17}N_3O_3$	81 (M + W)	+31.0	$C_{14}H_{17}N_3O$
8			g	192 (H + P)	−15.2	$C_{14}H_{17}N_3O_3$	82 (M + W)	−30.5	$C_{14}H_{17}N_3O$
9	183 (M)	+47.0[f]	$C_{10}H_7NO_2$	196 dec (W)	+75.5[h]	$C_{16}H_{19}N_3O_8$	208 dec (W)	−99.5[f]	$C_{16}H_{19}N_3O_6$
10	bp 192 (0.5 mm)	−41.2	$C_{14}H_{19}NO_3$	206 (M)	−304.2	$C_{20}H_{21}N_3O_4$	89 (M + W)	−8.9	$C_{20}H_{21}N_3O_2$
11	69 (M)		$C_{14}H_{19}NO_3$	219 (H + P)		$C_{20}H_{21}N_3O_4$	90 (M + W)		$C_{20}H_{21}N_3O_2$
12			g	190 (M)	−156.2	$C_{19}H_{19}N_3O_4$	159 (Z + P)	−92.3	$C_{19}H_{19}N_3O_2$
13			g	185 (M)	−89.0	$C_{13}H_{15}N_3O_4$	153 (H + P)	+18.5	$C_{13}H_{15}N_3O_2$
14	e	−44.5	$C_9H_{17}NO_3$	189 (M)	−131.6	$C_{15}H_{19}N_3O_4$	134 (Z + P)	+40.9	$C_{15}H_{19}N_3O_2$
15	83 (H + P)	−41.1	$C_{10}H_{19}NO_3$	192 (M)	−142.5	$C_{16}H_{21}N_3O_4$	158 (H + P)	+46.8	$C_{16}H_{21}N_3O_2$
16	e	−10.6	$C_{10}H_{19}NO_3$	167 (H + P)	−15.9	$C_{16}H_{21}N_3O_4$	123 (H + P)	+12.6	$C_{16}H_{21}N_3O_2$

[a] Series A-C, Scheme I. [b] Recrystallization solvents: E = ethanol, H = chloroform, M = methanol, P = petroleum ether (bp 40-60 °C), W = water, Z = benzene. [c] Unless otherwise stated, rotations were taken in chloroform at concentrations of 1-2%. [d] Elemental analyses (C, H, N), within ±0.4% of the theoretical values, were obtained and submitted for review. [e] Viscous oil, purified by column chromatography using silica gel and eluting with petroleum ether + diethyl ether solvent pair. [f] In water. [g] Has been characterized in ref 13. [h] In dimethylformamide.

Table II. Antibacterial Activity of 10B in Nutrient Agar

bacterium	MIC, μg/mL	CD_{50}, mg/kg, po
S. aureus	400	6.6 (5.359-7.775)[a]
P. vulgaris	400	4.1 (1.954-5.858)[a]

[a] Data in parentheses are 95% confidence limits.

in nutrient agar, with MIC and CD_{50} values as shown in Table II. Noteworthy is that the racemic modification of the (−)-ephedrine derivative (***11B***) was found to be almost inactive when tested as above.

The *primary* L-amino alcohol derivative (***12B***) was in vitro effective against *M. tuberculosis* (MIC = 20 μg/mL), while it was slightly active against *Ps. aeruginosa*. Compounds ***13B***–***16B*** were less potent than ***12B***, showing slight antibacterial activities against the above-mentioned species.

The hydrophilic glucosamine derivative (***9B***) as well as the hydrophobic adamantanamine derivatives (***3B*** and ***4B***) were inactive in these antibacterial screens.

In contrast to the aforementioned activity of the dioxides (B), the parent quinoxalines (C) were inactive as antibacterial agents.

Experimental Section

The amines and the amine hydrochlorides used in this study were biochemical grades (Merck, Aldrich, or NORSE) and were used without further purification. The L-amino alcohols were prepared by $LiAlH_4$ reduction of the appropriate L-α-amino acid following literature procedure (*12*). Melting points were determined on a Buchi SMP-20 apparatus (capillary method) and are uncorrected. Microanalyses were performed at the Laboratory of the late F. Pascher and E. Pascher, Bonn, West Germany. Optical rotations were taken on a Perkin-Elmer 141 polarimeter using a 10-cm tube. The NMR and mass spectrum instruments used in this study have been described previously (*5*, *6*). Compounds ***9B*** and ***9C*** were volatilized as their tetrakis(trimethylsiloxy) derivatives (for mass-spectral measurements).

The antibacterial screening tests were carried out at La Roche (England). The organisms selected were *Escherichia coli*, Mycobacterium *tuberculosis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, using the following media: nutrient agar, diagnostic sensitivity agar (Oxoid), and Davis minimal medium.

N-Acetoacetyl Amino Compounds (1A-16A). The *N*-acetoacetyl amino alcohols ***10A***, ***11A*** and ***14A-16A*** were prepared by the reaction of diketene (0.10 mol) with the appropriate free amino alcohol (0.11 mol) in a way analogous to that previously noted (*13*) for ***12A*** and ***13A***.

In the case of the *N*-acetoacetyl amines ***1A-4A*** the particular amine hydrochloride (0.10 mol) is first treated with 100 mL of cold 1 N methanolic NaOH; the precipitated NaCl is filtered off, and the methanolic filtrate is then treated, at 0–5 °C, with diketene as previously noted (*13*) for ***5A-8A***. The desired products were isolated in conventional manner and crystallized from the appropriate solvent.

In the case of ***9A***, a solution of D-(+)-glucosamine hydrochloride (21.8 g, 0.10 mol) in 100 mL of 10% aqueous $NaHCO_3$ is treated, at 0–5 °C, with diketene. The reaction mixture is stirred for 10 h at 20 °C and then lyophilized to give a white solid which is extracted with hot MeOH (5 × 60 mL). The combined methanolic extracts gave, upon cooling to room temperature, the desired *N*-acetoacetylglucosamine ***9A***. An analytically pure sample of ***9A*** is obtained by recrystallization from MeOH. Yields of ***1A-16A*** were in the range 60–86%.

(3-Methyl-2-quinoxaloyl)amine 1,4-Dioxides (1B-16B). A solution of benzofuroxan (*14*) (13.6 g, 0.10 mol) and the particular *N*-acetoacetyl amino compound (0.10 mol) in 100–200 mL of MeOH is treated, at 0–5 °C, with 50 mL of NEt_3, and the resulting solution is set aside at ambient temperature. After 1–6 h, the title 1,4-dioxides beging to separate as yellow solids, and the reaction is allowed to continue for 1–3 days. The product is then collected, washed with cold MeOH, and crystallized from the appropriate solvent. Yields of the pure 1,4-dioxides were in the range 50–78%. An exception is ***9B***, whose yield was only 12%. An improved yield (64%) of ***9B***, is however, achieved when DMF is used as a solvent medium in place of MeOH; evaporation of the solvents, in vacuo, gives a brown solid which is crystallized from H_2O (Norite). The mass spectra of ***1B-16B*** display characteristic peaks at the following *m/z* values: M^+, $(M - 16)^+$, $(M - 17)^+$, 187 (N_4-oxygenated quinoxaloyl ion); 171 (quinoxaloyl ion), 159 (N_4-oxygenated quinoxalinium ion), 143 (quinoxalinium ion). The $(M - CH_2OH)^+$ ions are also observed for ***12B-16B***. The ^1H NMR spectra (in Me_2SO-d_6) are in accord with the assigned structures and exhibit characteristics of the 2-carboxamidoquinoxaline 1,4-dioxide

moeity (*9*, *10*). The C_3–CH_3 proton signal has a δ value of ~2.80 for the aliphatic series ***13B–16B***, whereas it is only ~2.48 for the aromatic analogue ***12B***.

N*-(3-Methyl-2-quinoxaloyl) Amines (1C–16C).** These were obtained by deoxygenation of the corresponding quinoxaline 1,4-dioxides (0.10 mol) with excess $Na_2S_2O_4$ (69.6 g, 0.40 mol) in refluxing aqueous EtOH, following standard procedures (*15*). The title compounds are precipitated from the reaction mixture by cooling and dilution with water, collected, dried, and crystallized from the appropriate solvent. Yields of the pure quinoxalines were in the range 45–70%. The mass spectra of ***1C–16C show characteristic peaks at the following *m/z* values: M^+, 171, 143. The $(M - CH_2OH)^+$ ions are also observed for ***12C–16C***. The ^1H NMR spectra (in Me_2SO-d_6) are in agreement with the assigned structures. The C_3–CH_3 δ value is ~2.90 for ***12C–16C***.

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Registry No. **1A**, 63664-38-0; **1B**, 88996-65-0; **1C**, 88996-79-6; **2A**, 88996-62-7; **2B**, 88996-66-1; **2C**, 88996-80-9; **3A**, 58102-37-7; **3B**, 88996-67-2; **3C**, 88996-81-0; **4A**, 63664-40-4; **4B**, 88996-68-3; **4C**, 88996-82-1; **5A**, 63664-41-5; **5B**, 88996-69-4; **5C**, 88996-83-2; **6A**, 63664-42-6; **6B**, 88996-70-7; **6C**, 88996-84-3; **7A**, 64401-27-0; **7B**, 88996-71-8; **7C**, 88996-85-4; **8A**, 64401-28-1; **8B**, 88996-72-9; **8C**, 88996-86-5; **9A**, 63664-39-1; **9B**, 88996-73-0; **9C**, 88996-87-6; **10A**, 63701-36-0; **10B**, 81485-17-8; **10C**, 88996-88-7; **11A**, 63664-37-9; **11B**, 89063-57-0; **11C**, 89063-58-1; **12A**, 63664-36-8; **12B**, 88996-74-1; **12C**, 88996-89-8; **13A**, 64401-30-5; **13B**, 88996-75-2; **13C**, 88996-90-1; **14A**, 63664-35-7; **14B**, 88996-76-3; **14C**, 88996-91-2; **15A**, 88996-63-8; **15B**, 88996-77-4; **15C**, 88996-92-3; **16A**, 88996-64-9; **16B**, 88996-78-5; **16C**, 88996-93-4; [*R*-(*R**,*S**)]-MeNHCH(CH_3)CH(OH)Ph, 299-42-3; (±)-(*R**,*S**)-MeNHCH(CH_3)CH(OH)Ph, 90-81-3; diketene, 674-82-8; (*S*)-2-amino-3-methylbutanol, 2026-48-4; (*S*)-2-amino-4-methylpentanol, 7533-40-6; [*S*-(*R**,*S**)]-2-amino-3-methylpentanol, 88996-94-5; 3-(2-aminoethyl)indole hydrochloride, 343-94-2; 4-(2-aminoethyl)imidazole hydrochloride, 55-36-7; 1-adamantanamine hydrochloride, 665-66-7; 2-adamantanamine hydrochloride, 10523-68-9; D-(+)-glucosamine hydrochloride, 66-84-2; benzofuroxan, 674-82-8.

Literature Cited

(1) Ochia, E. "Aromatic Amine Oxides"; Elsevier: Amsterdam, 1967.
(2) Katritsky, A. H.; Lagowski, J. M. "Chemistry of the Heterocyclic *N*-Oxides"; Academic Press: New York, 1971.
(3) Pfizer, Inc., U.S. Patent 3 948 911, 1976.
(4) Pfizer Inc., U.S. Patent 4 007 184, 1977.
(5) Pfizer Inc., U. S. patent 4 039 540, 1977.
(6) AG. Ciba-Geigy, German Patent 2 701 707, 1977.
(7) Research Corp., British Patent 1 308 370, 1973.
(8) Haddadin, M. J.; Issidorides, C. H. *Heterocycles* **1976**, *4*, 767-816.
(9) EL-Abadelah, M. M.; Sabri, S. S.; Nazer, M. Z.; Za'ater, M. F. *Tetrahedron* **1976**, *32*, 2931-8.
(10) EL-Abadelah, M. M.; Sabri, S. S.; Tashtoush, H. I. *Tetrahedron* **1979**, *35*, 2571-6.
(11) Henry, J. B. "Clinical Diagnosis and Management by Laboratory Methods"; Saunders: Philadelphia, PA, 1979; Vol. II, p 1622.
(12) Vogl, O.; Pöhm, M. *Monatsh. Chem.* **1952**, *83*, 541-3.
(13) Sabri, S. S.; EL-Abadelah, M. M.; Za'ater, M. F. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1356-9.
(14) Mallory, F. M. In "Organic Synthesis"; Wiley: New York, 1967; Collect. Vol. IV, p 74.
(15) Haddadin, M. J.; Zahr, G. E.; Rawdah, T. N.; Chelhot, N. C.; Issidorides, C. H. *Tetrahedron* **1974**, *30*, 659-66.

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Potential Central Nervous System Active Agents. 3. Synthesis of Some Substituted Benzamides and Phenylacetamides

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The preparation and spectral properties (IR, ^1H NMR) are given for 45 benzamides and 10 phenylacetamides substituted on nitrogen with allyl, benzhydryl, benzyl, or cyclopropyl groups, and variously substituted on the acyl part with halo, methoxyl, methyl, or nitro groups. The benzamide derivatives were synthesized by the Schotten–Baumann method, and the phenylacetamide derivatives were prepared by heating the appropriate *N*-benzhydrylammonium salt in *o*-xylene. Thirty-one of the compounds are new.

In the preceding communications (*1*, *2*) the synthesis and the spectroscopic properties (IR, mass spectra, ^1H NMR) of several aromatic *N*-benzyl amides were reported. Presented in the current communication are the synthesis and the spectroscopic data for 45 benzamides and 10 phenylacetamides substituted on nitrogen with allyl, benzhydryl, benzyl, or cyclopropyl groups, and variously substituted on the acyl part with halo, methoxyl, methyl, or nitro groups. The benzamide derivatives were prepared by the Schotten–Baumann method in anhydrous benzene, and the phenylacetamide derivatives were synthesized from their corresponding *N*-benzhydrylammonium salts in boiling *o*-xylene as has been described earlier (*1*). With the exception of compounds Ia, VIa,b,h, and VIIa, all derivatives bearing the *N*-benzhydryl and *N*-cyclopropyl groups described herein are previously unreported. Compounds IIb,g, IIId, and Vb,e,f, bearing the *N*-allyl, *N*,*N*-diallyl, or *N*,*N*-dibenzyl groups, are also unreported. The spectroscopic data (IR, ^1H NMR) not hitherto described in the literature are reported in this publication. The experimental and IR data on all the compounds are summarized in Table I, and those of the ^1H NMR data are given in Table II. Satisfactory elemental analyses (±0.4% for C, H, N, and halogens, where present) were obtained for all compounds.

The structures of these amides were established on the basis of analytical and spectroscopic data. These compounds have been submitted for biological screening, and results will be published elsewhere.

Experimental Section

The reagents used in these experiments were of commercial grade. Mass spectra were determined on a Varian-MAT CH-5 spectrometer at 70 eV, by Messrs. J. C. Cook and M. Cochran, Mass Spectroscopy Laboratory, University of Illinois, Urbana

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