The crystal had approximate dimensions of 0.25 × 0.20 × 0.10 mm. Preliminary examination and data collection were performed with Cu Kα radiation (λ = 1.541 84 Å) on an Enraf Nonius CAD4 computer-controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 23 reflections in the range $9 < \theta < 26°$, measured by the computer-controlled diagonal-slit method of centering. The monoclinic cell parameters and calculated volume are a = 7.895 (1) Å, b = 11.008 (2) Å, c = 10.501 (1) Å, β = 95.50 (1)°, V = 908.4 Å^3. For Z = 2 and FW = 393.31 the calculated density is 1.44 g/cm^3. The space group was determined to be $P2(1)$. A total of 2068 reflections were collected, of which 1961 were unique and not systematically absent. The structure was solved by direct methods. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full-matrix least squares. Atomic coordinates are listed in Table II.

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Novel Nonnarcotic Analgesics with an Improved Therapeutic Ratio. Structure–Activity Relationships of 8-(Methylthio)- and 8-(Acylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines

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Conversion of the 8-phenolic 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines to the corresponding 8-thiophenolic analogues was achieved by three different routes. Diazotization of 8-amino-2,6-methano-3-benzazocine (**2**) followed by the reaction with CH_3SNa afforded 8-(methylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**3**). Another route using Grewe cyclization was also examined for the synthesis of **3**. As the most effective route, Newman–Kwart rearrangement of benzazocines was selected and closely investigated. 8-(*N*,*N*-Dimethylthiocarbamoyl)oxy derivatives (**6a–e**) rearranged to 8-(*N*,*N*-dimethylcarbamoyl)thio derivatives (**7a–e**) in good yields. Reductive cleavage of **7a–e** and subsequent methylation or acylations gave the title compounds (**3**, **8–24**). Although analgesic activities of sulfur-containing benzazocines decreased compared to the corresponding hydroxy compounds, the *N*-methyl derivative (*S*-metazocine, **8**) showed potent analgesic activity.

Recently heterocyclic analogues of 2,6-methano-3-benzazocines, pyridomorphans,[1] thienomorphans,[2] pyrrolomorphans,[3] and thiazolomorphans[4] were reported. However, only limited examples of chemical modifications of the 8-hydroxy group of the skeleton have appeared, e.g. simple alkylation, acylation, or substitution with halogeno groups.[5] Very recently, Wentland et al. reported the synthesis and pharmacology of 8-aminocyclazocines,[6] but no other functionalized benzomorphans at the 8-position have appeared so far.

It has been considered that an interaction between a phenolic group of a narcotic compound with a sterically rigid chemical structure and an opioid receptor binding site is necessary to initiate its biological activity.[7] Therefore, we undertook the synthesis of 8-mercapto-benzomorphans[8] and evaluation of the pharmacological activity with the concept of bioisosterism[9] between oxygen and sulfur.

Chemistry. We accomplished the introduction of sulfur groups by three different routes (A–C). In route A we selected 8-nitro-3,6(e),11(a)-trimethyl-2,6-methano-3-benzazocine (**2**)[10] as the starting material. Reduction of **2** and treatment with $NaNO_2$ in dilute H_2SO_4 solution followed by the reaction with aqueous CH_3SNa afforded 8-methylthio derivative **3** in 49% yield. The *S*-methyl signal appeared at δ 2.47, and the structure of **3** was established by physicochemical data such as mass spectra. Although the introduction of the sulfur group was successful, this method cannot be applied to *N*-aralkyl-2,6-

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Table I. 1,2,3,4,5,6-Hexahydro-8-[(*N*,*N*-dimethylthiocarbamoyl)oxy]-6(e),11(a)-dimethyl-1,2,6-methano-3-benzazocines (**6a–f**)

compd	R	yield, %	formula[a]	mp, °C	recrystn solvent[b]	NMR ($CDCl_3$) δ: Me_2N
6a	CH_3	85	$C_{18}H_{26}N_2OS$	124–126	A	3.33, 3.46
6b	$CH_2CH_2C_6H_5$	100	$C_{25}H_{32}N_2OS\cdot HCl$	203–205	B	3.28, 3.46
6c	$CH_2CH{=}CMe_2$	84	$C_{22}H_{32}N_2OS\cdot C_2H_2O_4$[c]	187–189	B	3.33, 3.46
6d	CH_2CH_2-thienyl	81	$C_{23}H_{30}N_2OS_2\cdot HCl$	229–232[d]	C	3.33, 3.46
6e	$CH_2C_6H_5$	72	$C_{24}H_{30}N_2OS\cdot HBr$	185–188	B	3.30, 3.43
6f	CH_2-c-C_3H_7	96	$C_{21}H_{30}N_2OS\cdot HCl$	232–234[d]	B	3.30, 3.43

[a] Satisfactory C, H, and N analyses (within +0.4% of theoretical values) were obtained unless otherwise noted. [b] Key: A = H_2O–MeOH; B = MeOH–acetone; C = MeOH–Et_2O; D = EtMeCO; E = acetone–Et_2O; F = EtOH–Et_2O; G = acetone; H = EtMeCO–Et_2O; I = EtOH; J = MeOH–AcOEt; K = acetone–AcOEt. [c] Oxalate. [d] Decomposition.

Table II. 1,2,3,4,5,6-Hexahydro-8-[(*N*,*N*-dimethylcarbamoyl)thio]-6(e),11(a)-dimethyl-2,6-methano-3-benzazocines (**7a–e**)

compd	R	conditions: temp	conditions: min	yield, %	formula[a]	mp, °C	recryst[b] solvent	NMR ($CDCl_3$) δ: Me_2N
7a	CH_3	300	5	92	$C_{18}H_{26}N_2OS\cdot C_2H_2O_4$[c]	202–203	C	3.04
7b	$CH_2CH_2C_6H_5$	320	6	96	$C_{25}H_{32}NOS\cdot HCl$	193–195	B	3.03
7c	$CH_2CH{=}CMe_2$	325	0.5	11	$C_{22}H_{32}N_2OS\cdot C_2H_2O_4\cdot 0.5H_2O$[d]	95–98	D	3.08
7d	CH_2CH_2-thienyl	310	5	96	$C_{25}H_{32}NOS_2\cdot HCl$[e]	175–178	E	3.05
7e	$CH_2C_6H_5$	315	4	74	$C_{24}H_{30}NOS\cdot C_2H_2O_4\cdot 0.5H_2O$[d]	165–168	F	3.06

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] Oxalate. [d] Oxalate hemihydrate. [e] C: calcd, 61.24; found, 60.82.

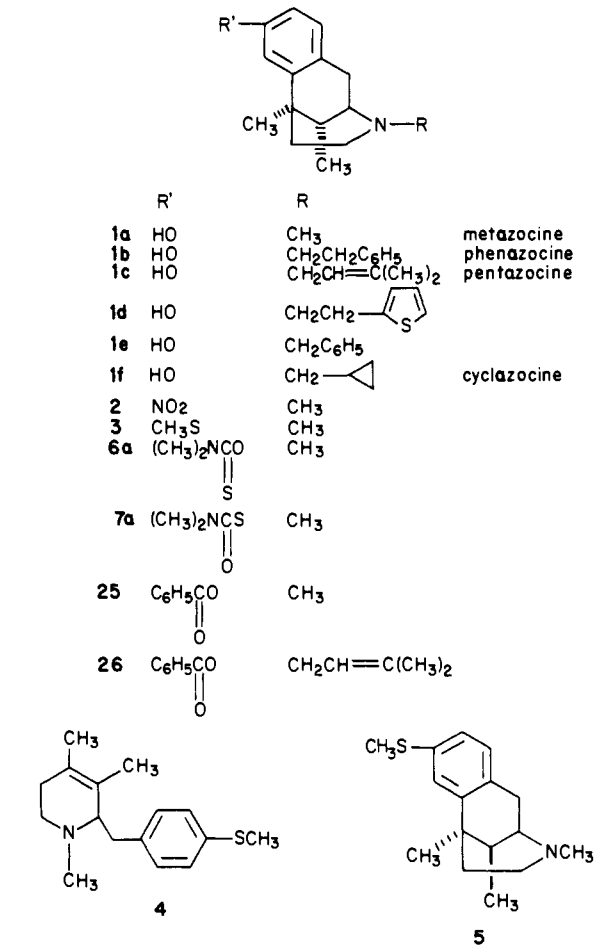
methano-3-benzazocines such as 8-deoxyphenazocine, because N-aromatic substituents would be nitrated (Chart I).

We then turned our attention to the Grewe synthesis as the second route (route B). Grignard reaction of [4-(methylthio)benzyl]magnesium chloride[11] with *N*-methyl-3,4-lutidinium iodide and subsequent reduction with $NaBH_4$ afforded tetrahydropyridine derivative **4** in 44% yield. Cyclization conditions of **4** were investigated. Only when polyphosphoric acid was used at 135–140 °C was the cyclized product **3** obtained in 9.3% yield together with its isomer **5** in 1.1% yield. The major isomer **3** (fumarate mp 204–205 °C) was identical with the sample prepared as described above by the comparison of NMR and IR spectra. However, total yield by this route was low.

Next, in order to exploit a more efficient and suitable route, Newman–Kwart rearrangement[12] was applied to the synthesis of sulfur-containing 2,6-methano-3-benzazocines (route C). This plan was started from various N-substituted 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-benzazocines (**1a–f**). The reaction of *N*,*N*-dimethylthiocarbamoyl chloride with sodium salts of **1a–f** in DMF afforded (*N*,*N*-dimethylthiocarbamoyl)oxy derivatives (**6a–f**) in good yields. As the Newman–Kwart thermal rearrangement was reported to proceed under a variety of conditions from 130 to 335 °C for 20 min,[12] the optimum conditions for **6a–f** were investigated. Compound **6a** (neat) was heated under N_2 in a metal bath (Tables I and II).

Rearrangement of **6a** to **7a** could be monitored by thin-layer chromatography (TLC) or NMR spectroscopy. The 8-dimethylamino absorptions at δ 3.33 and 3.46 decreased, and a sharp singlet of 8-[(dimethylamino)carbamoyl]thio group increased gradually as the reaction proceeded. Optimum conditions of **6a** were at 300 °C for 5 min. Likewise, optimum reaction conditions of **6b–e** and **7b–e** were determined as shown in Table II. Among compounds **6a–e**, **6e** was sensitive to heat and gave **7e** in 74% yield with some decomposition at 315 °C for 5 min. The *N*-prenyl (**6c**) and *N*-cyclopropylmethyl derivative (**6f**) were readily decomposed to unidentified tars. The conditions for **6d** were settled at relatively high temperature and very short time (325 °C, 30 s) to afford **7d** in 11% yield after careful chromatographic separation from recovered **6d**.

Chart I



The SH group is generally unstable chemically and metabolically, so the protection of the SH group was accomplished without isolation of thiols by the reduction of **7** with $LiAlH_4$ and successive treatment with appropriate RCOCl, alkyl halides, or Me_2SO_4, and target compounds

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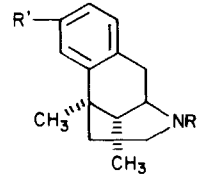
Table III. 8-(Acylthio)- and 8-(Methylthio)-1,2,3,4,5,6-hexahydro-6(e),11(a)-dimethyl-2,6-methano-3-benzazocines (8–24)



compd	R	R′	yield, %	formula[a]	mp, °C	recrystn[b] solvent	analgesic act.: ED_{50} (95% CL)
8	CH_3	C_6H_5COS	86	$C_{22}H_{25}NOS \cdot C_4H_4O_4 \cdot H_2O$[c]	153–154	G	1.05 (0.66–1.68)
9	CH_3	4-ClC_6H_4COS	65	$C_{22}H_{24}ClNOS \cdot C_4H_4O_4$[d]	165–166	D	2.8 (0.99–7.90)
10	CH_3	4-$CH_3OC_6H_4COS$	54	$C_{23}H_{27}NO_2S \cdot C_4H_4O_4$[d]	201–202	B	4.8 (2.15–10.7)
11	CH_3	Me_3CCOS	33	$C_{20}H_{29}NOS \cdot C_4H_4O_4$[d,e]	182–185	H	6.4 (3.30–12.4)
12	CH_3	CH_3COS	48	$C_{17}H_{23}NOS \cdot 0.5C_4H_4O_4 \cdot H_2O$[f]	151–153[g]	G	4.5 (1.80–11.3)
13	$CH_2CH_2C_6H_5$	C_6H_5COS	78	$C_{29}H_{31}NOS \cdot HCl$	220–223	G	1.7 (1.00–2.87)
14	$CH_2CH_2C_6H_5$	4-ClC_6H_4COS	67	$C_{29}H_{30}NClOS \cdot HCl$	220–222	B	40%—20 mg/kg
15	$CH_2CH_2C_6H_5$	4-$CH_3OC_6H_4COS$	74	$C_{30}H_{33}NO_2S \cdot HCl$[h]	219–221	B	5.3 (2.64–10.65)
16	$CH_2CH_2C_6H_5$	Me_3CCOS	64	$C_{27}H_{35}NOS \cdot HCl$	247–249[g]	B	5.2 (2.64–10.65)
17	$CH_2CH_2C_6H_5$	C_2H_5COS	93	$C_{25}H_{31}NOS \cdot C_4H_4O_4$[d]	166–167	D	7.0 (5.9–8.30)
18	$CH_2CH_2C_6H_5$	C_2H_5OCOS	92	$C_{25}H_{31}NO_2S \cdot C_4H_4O_4$[d]	160–162	H	18.5 (13.64–25.42)
19	$CH_2CH{=}CMe_2$	C_6H_5COS	98	$C_{26}H_{31}NOS \cdot C_4H_4O_4$[d,i]	175–177	E	4.0 (2.0–8.0)
20	$CH_2CH{=}CMe_2$	4-ClC_6H_4COS	66	$C_{26}H_{30}NOS \cdot C_4H_4O_4 \cdot 0.5H_2O$[j]	169–171	D	6.0 (2.51–14.3)
21	$CH_2CH{=}CMe_2$	4-$CH_3OC_6H_4COS$	57	$C_{27}H_{33}NO_2 \cdot C_4H_4O_4$[d]	180–181	D	5.3 (2.64–10.65)
22	$CH_2CH{=}CMe_2$	Me_3CCOS	53	$C_{24}H_{35}NOS \cdot C_4H_4O_4$[d]	192–194	D	50%—10 mg/kg
23	2-(thienyl)ethyl	C_6H_5COS	84	$C_{27}H_{29}NOS_2 \cdot C_4H_4O_4$[d]	207–209	B	40%—20 mg/kg
24	$CH_2C_6H_5$	C_6H_5COS	72	$C_{28}H_{29}NOS \cdot HCl$	191–193	K	30%—20 mg/kg
25	CH_3	C_6H_5COO	77.5	$C_{22}H_{25}NO_2 \cdot C_4H_4O_4$[d]	219–221[g]	J	*k*
26	CH_2CHCMe_2	C_6H_5COO	40	$C_{26}H_{31}NO_2 \cdot C_4H_4O_4$[d]	192–193	G	2.6 (1.63–4.16)
metazocine (**1a**)							0.46 (0.29–0.73)
phenazocine (**1b**)							0.135 (0.082–0.194)
pentazocine (**1c**)							1.6 (1.01–2.53)
N-[2-(thienyl)ethyl]normetazocine (**1d**)							0.071 (0.054–0.093)
morphine							0.52 (0.33–0.83)

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] Fumarate monohydrate. [d] Fumarate. [e] C: calcd, 64.40; found, 63.98. [f] Hemifumarate hydrate. [g] Decompostion. [h] N: calcd, 2.76; found, 2.31. [i] C: calcd, 69.07; found, 68.62. [j] Fumarate hemihydrate. [k] This compound showed low solubility in water. Analgesic activity was tested by po administration in mice: ED_{50} 1.7 (0.383–3.50) (cf. morphine ED_{50} 1.2 (0.78–1.84)).

Table IV. Optically Active 8-(Benzoylthio)-1,2,3,4,5,6-hexahydro-6(e),11(a)-dimethyl-2,6-methano-3-benzazocines

compd	yield, %	formula[a]	mp, °C	recryst[b] solvent	$[\alpha]_D$ (c EtOH)	analgesic act.: ED_{50} in mice
S-(+)-6a	64	$C_{18}H_{26}N_2OS$	126	A	+53.3 (0.195)	
R-(−)-6a	83	$C_{18}H_{26}N_2OS$	127	A	−54.4 (0.982)	
S-(+)-6c	77	$C_{22}H_{32}N_2OS$	104–106	A	+102.7 (0.823)	
R-(−)-6c	75	$C_{22}H_{32}N_2OS$	106–107	A	−102.2 (1.699)	
S-(+)-7a	73	$C_{18}H_{24}N_2OS \cdot C_2H_2O_4$[c]	184	J	+30.2 (0.586)	
R-(−)-7a	85	$C_{18}H_{24}N_2OS \cdot C_2H_2O_4$[c]	185	J	−30.3 (0.221)	
S-(+)-7c	8	$C_{22}H_{32}N_2OS \cdot C_2H_2O_4$[d]	120–124	F	+66.3 (0.502)	
R-(−)-7c	8	$C_{22}H_{32}N_2OS \cdot C_2H_2O_4$[d]	120–124	F	−66.0 (0.421)	
S-(+)-8	86	$C_{22}H_{25}NOS \cdot C_4H_4O_4 \cdot 0.5H_2O$[e]	132–133	D	+34.0 (1)	30% −10 mg
R-(−)-8	84	$C_{22}H_{25}NOS \cdot C_4H_4O_4 \cdot 0.5H_2O$[e]	132–133	D	−34.6 (1)	1.0 (0.55–1.82)
S-(+)-19	45	$C_{26}H_{31}NOS \cdot C_4H_4O_4$	101–103	F	+76.7 (1)	20%–10 mg/kg
R-(−)-19	56	$C_{26}H_{31}NOS \cdot C_4H_4O_4$	100–102	F	−77.3 (0.4)	0.74 (0.42–1.31)
S-(+)-1a						20–30%
R-(−)-1a						0.27 (0.16–0.45)
S-(+)-1c						20%–10 mg/kg
R-(−)-1c						0.36 (0.20–0.60)

[a] See footnote a, Table I. [b] See footnote b, Table I. [c] Oxalate. [d] Fumarate hemihydrate. [e] Fumarate.

(3, 8–24) were obtained in excellent yields as shown in Table III. Reduction of 7 and methylation with Me_2SO_4 gave 3 in 91% yield.

Consequently, the third method was superior to the preceding two with respect to total yields and applicability to benzomorphans with various nitrogen substituents.

Optically active compounds of 8 and 19 were also synthesized by route C starting from optically active 1a[13] and 1c.[14] Results are shown in Table IV. For pharmacological reference O-benzoylmetazocine (25) and O-benzoylpentazocine (26) were prepared by benzoylation of 1a and 1c, respectively.

Analgesic Activity and Discussion. Analgesic activities were evaluated by acetic acid writhing inhibition methods in mice. The onsets of analgesia of sulfur-containing 3-benzazocines are relatively slow, and the maximum effects appeared 40 min after sc administration. Peak times of activities were 30 and 25 min for morphine and metazocine (1a), respectively. The results are summarized in Tables III and IV. In the case of the N-methyl derivatives (8–12) benzoylthio derivative 8 showed the most potent activity. The activity of 8 was about $^1/_2$ that of morphine or metazocine and was the same as that of pentazocine.

Both p-chloro- and p-methoxy-substituted S-benzoyl derivatives showed weak activity compared with the original compounds. The bulky pivaloylthio group (derivative 11) decreased the activities.

It is reported[15] that acetoxybenzomorphan is 2 times as potent as metazocine because the acetoxy group might be easily hydrolyzed to the hydroxy moiety in vivo after its efficient transport to the active site. Enhanced activity was observed in the case of (acetylthio)deoxymetazocine (12).

It is well-known that analgesic activities of benzomorphans are significantly affected by their N-substituent groups. The activity of phenazocine (1b)[13] is greater than that of metazocine. 2-(Thienyl)ethyl derivative 1d is one of the most potent analgesics in the benzomorphan series. Conversion of the 8-phenolic hydroxy group in a series of metazocine derivatives to a sulfur group slightly decreased analgesic activity. These lowering effects were more significant for phenazocine derivatives (13–18). In the case of 2-(thienyl)ethyl derivative 23, activity completely disappeared. In considering the effects of acyl groups, the activity profiles of the N-phenethyl (13–18) and the prenyl derivatives (19–22) were almost the same as with N-methyl derivatives. Benzoyl derivatives 13 and 19 showed most potent activities in a series of S-acyl derivatives.

Table V. Opiate Receptor Binding Assay ([^{3}H]Naloxone) and the Change of ED_{50} Values by the Simultaneous Injection of Drug and Naloxone (0.2 mg/kg) in Mice

	ORB: IC_{50}, nM	ED_{50} ratio (with/without Naloxone)
8	1530	1.7
25	107	6.4
pentazocine	53	3.4
morphine	8.6	8.5

In the optically active series of 8 and 19, analgesic activity predominantly resided in the R-(−) isomers like the original compounds.

It is noted that none of the sulfur-containing benzomorphans showed a Straub tail reaction in contrast to morphine and metazocine (1a), and the analgesic activity of 8 was not antagonized by naloxone (Table V). From these results we selected 8 (S-metazocine) as a promising nonnarcotic analgesic.

The results of opiate receptor binding assay ([^{3}H]naloxone) using the rat brain membrane are shown in Table V. The affinity of 8 for the receptor was weaker than that of pentazocine.

It is considered that a possible mode of metabolic inactivation of benzomorphans containing a phenolic hydroxyl is conjugation of the hydroxyl with glucuronic acid.[6] So it is anticipated that the replacement of the hydroxyl group by another functional group would give an analgesic without this type of metabolic inactivation. In the case of 8-amino-8-deoxycyclazocine,[6] the duration of activity was reported to be comparable to that of cyclazocine. However, there was no parallelism[16] of the analgesic activities between the title compounds and their original 8-hydroxy derivatives. The results of receptor binding suggest that the mode of the receptor interaction for S-metazocine (8) is different from that of metazocine.

S-Metazocine showed no appreciable respiratory depression (rats), gastrointestinal constipation (mice), or change of body temperature and blood glucose level (rabbits). The toxicity of S-metazocine (LD_{50} 125 mg/kg

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in mice ip) was lower than that of metazocine (81 mg/kg).

Further pharmacological evaluations are now in progress, and these results will be published in a separate paper.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (film) were recorded on a Jasco A-1 spectrophotometer. NMR spectra were obtained for solutions in $CDCl_3$ on a Hitachi R-20B spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a JEOL JMS-D 300 spectrometer with a direct-insertion probe at 70 eV.

Synthesis of 8-(Methylthio)-1,2,3,4,5,6-hexahydro-3,6-(e),11(a)-trimethyl-2,6-methano-3-benzazocine (3). Method A. 8-Nitro-1,2,3,4,5,6-hexahydro-3,6(e),11(a)-trimethyl-2,6-methano-3-benzazocine (**2**)[10] was hydrogenated with H_2 in the presence of 5% Pd–C in methanol for 2 h. The filtrate was evaporated. To an ice-cooled solution of the 8-amino derivative in 3.2 mL of 3 N H_2SO_4 was added 0.149 g of $NaNO_2$ in 1 mL of water and the resultant mixture stirred for 1 h. The solution was added to CH_3SNa (0.88 g) in 5 mL of water for 15 min. The mixture was stirred at 70 °C for 0.5 h and then poured into dilute NH_4OH solution. The ethereal extracts were dried ($MgSO_4$) and evaporated. The residue was separated by TLC on silica gel (ether–hexane–EtN_3 (5:10:1) as solvents) to give 0.33 g of **3** as a colorless oil: yield 49%; NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 7 Hz, $C_{11}CH_3$), 1.37 (3 H, s, C_6CH_3), 2.39 (3 H, s, NCH_3), 2.47 (3 H, s, SCH_3), 6.99–7.27 (3 H, m, aromatic H). Fumarate was obtained as colorless prisms from EtOH–ether, mp 206 °C. Anal. ($C_{16}H_{23}NS\cdot C_4H_4O_4$) C, H, N.

Method B (from 4). The solution of 16.7 g of 4-(methylthio)benzyl chloride[11] in 70 mL of THF was added to 3.1 g of magnesium in 50 mL of THF. After refluxing for 1 h and cooling to 30 °C, 17.4 g of N-methyl-3,4-lutidinium iodide was added portionwise and the mixture refluxed for 20 min. The solution was poured into ice-cooled aqueous NH_4Cl and extracted with ether. Ethereal extract was dried and evaporated to give 19 g of crude oil. The oil was dissolved in 150 mL of MeOH, 2.7 g of $NaBH_4$ was added portionwise, and the solution was refluxed for 1 h, evaporated in vacuo, and extracted with ether–H_2O. Ethereal extract was dried and evaporated to give an oil: 8.0 g (44%); NMR ($CDCl_3$) δ 1.60 (6 H, br s, 2 3,4-CH_3), 2.35 (3 H, s, NCH_3), 2.46 (3 H, s, SCH_3), 7.17 (4 H, br s, aromatic H); oxalate mp 130–131 °C. Anal. ($C_{16}H_{23}NS\cdot C_2H_2O_4$) C, H, N.

The mixture of 15 g of polyphosphoric acid and 2.8 g of **4** was heated at 135–140 °C for 5.5 h and poured into ice-cooled NH_4OH. Chloroform extract was dried ($MgSO_4$) and evaporated to give a yellow oil. The oil was chromatographed on silica gel (ether–hexane–Et_3N (1:25:1)) to give **3** (41 mg, 9.3%) as an oil and **5** (5 mg, 1.1%). Fumarate of **3** was crystallized from EtOH–ether as colorless prisms, mp 204–205 °C. NMR and IR spectra of **3** were identical with the sample prepared by method A. NMR data of **5** ($CDCl_3$): δ 1.23 (3 H, d, J = 7 Hz, $C_{11}CH_3$), 1.31 (3 H, s, C_6CH_3), 2.33 (3 H, s, NCH_3), 2.45 (3 H, s, SCH_3), 6.90–7.32 (3 H, m, aromatic H). Compound **5** was crystallized as the fumarate, mp 184–186 °C dec from EtOH–ether. Anal. ($C_{16}H_{23}NS\cdot C_4H_4O_4$) C, H, N.

Method C. To the 3 ml of ethereal solution of **7a** (106 mg) was added 38 mg of $LiAlH_4$ in one portion and the resultant mixture stirred for 45 min. To the suspension was added 147 mg of Me_2SO_4 in 1.5 mL of ether dropwise in 2 min. After stirring for 45 min, dilute NaOH was added and the resultant mixture was extracted with ether, dried (K_2CO_3), and evaporated to give 79 mg of **3** as colorless oil. Yield was 91%. The NMR spectrum of the oil was identical with that of a sample prepared by method A.

General Procedure for the Syntheses of 8–24. Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methano-3,6(e),11(a)-trimethyl-8-[(*N*,*N*-dimethylthiocarbamoyl)oxy]-3-benzazocine (6a). To 60 mL of DMF solution of 1.5 g of **1a** was added 0.35 g of NaH and the mixture was stirred for 1 h at room temperature. At 10 °C, 20 mL of DMF solution of 1.25 g of dimethylthiocarbamoyl chloride was added. The mixture was heated at 80 °C for 1 h, cooled, poured into 1% KOH solution, and extracted with benzene–hexane (4:1) and then with 5% HCl. The HCl extracts were made alkaline with 10% KOH, and the ethereal extracts were dried ($MgSO_4$) and evaporated to give 1.7 g of **6a** as crystalline product: prisms from AcOEt; mp 124–125.5 °C; NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz, $C_{11}CH_3$), 1.37 (3 H, s, C_6CH_3), 2.39 (3 H, s, NCH_3), 3.30, 3.43 (3 H, 3H, each s, 2 NCH_3), 6.65–7.25 (3 H, m, aromatic H). Anal. ($C_{18}H_{26}N_2OS$) C, H, N.

Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methano-3,6(e),11-(a)-trimethyl-8-[(*N*,*N*-dimethylcarbamoyl)thio]-3-benzazocine (7a). Newman–Kwart Rearrangement of 6a. A 100-mL round-bottom flask containing 5.0 g of **6a** was kept in a metal bath at 300 °C for 5 min under N_2. The flask was then cooled, and the oil was chromatographed on silica gel (ether–hexane–Et_3N (1:10:1) as eluents) to give 4.6 g of **7a** as colorless oil: 92%; NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 7 Hz, $C_{11}CH_3$), 1.35 (3 H, s, C_6CH_3), 2.35 (3 H, s, NCH_3), 3.01 (6 H, s, 2 NCH_3), 6.85–7.25 (3 H, m, aromatic H); IR (film) 1675 cm^{-1} (C=O). The oxalate, after recrystallization from MeOH–Et_2O, melted at 201.5–202.5 °C. Anal. ($C_{18}H_{26}N_2OS\cdot C_2H_2O_4$) C, H, N.

Synthesis of 8-(Benzoylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3,6(e),11(a)-trimethyl-3-benzazocine (8). To the suspension of 0.31 g of $LiAlH_4$ in THF (20 mL) and ether (30 mL) was added 1.3 g of **7a** in THF (30 mL) and ether (45 mL) and the resultant mixture stirred for 2 h. After it was cooled to 0 °C, 2.87 g of benzoyl chloride in 30 mL of ether was added dropwise and the mixture stirred for 0.5 h. The mixture was poured in dilute K_2CO_3. After filtration with Celite, the ethereal extracts were dried ($MgSO_4$), evaporated, and chromatographed on silica gel (benzene and then ether–Et_3N (10:1)) to give 1.23 g (86%) of crystalline **8**: NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz, $C_{11}CH_3$), 1.40 (3 H, s, C_6CH_3), 2.44 (3 H, s, NCH_3), 7.00–7.65 (6 H, m, aromatic H), 7.90–8.15 (2 H, m, aromatic H); IR (KBr) 1675 cm^{-1} (C=O). The fumarate monohydrate was recrystallized from acetone, yielding colorless prisms mp 153–154 °C. Anal. ($C_{22}H_{25}NOS\cdot C_4H_4O_4\cdot H_2O$) C, H, N.

Synthesis of **3** by this method was shown above.

Analgesic Activities. AcOH Writhing by All-or-None Method. Ten mice were used in each group. The drugs were administered by the sc or po routes. The sc administration was performed simultaneously with ip injection of 0.7% AcOH. At 15 min after the injection of AcOH, writhing response was observed for 5 min at intervals of 15 min totaling four times; mice showing the writhing more than one time within 5 min were regarded as no analgesic effect.

Opiate Receptor Binding Assay. Binding assays were performed in homogenates of rat brain (P_2 fraction) by the rapid-filtration method. The activities against 5×10^{-9} M of [^{3}H]-naloxone were evaluated by constructing the dose–response curves, and the concentration giving 50% inhibition (IC_{50}) was calculated by linear regression from log Probit plots.

Registry No. (±)-**1a**, 58640-79-2; (+)-**1a**, 67009-58-9; (−)-**1a**, 21286-60-2; (±)-**1b**, 56942-74-6; (±)-**1c**, 21820-34-8; (+)-**1c**, 7361-76-4; (−)-**1c**, 7488-49-5; (±)-**1d**, 64023-87-6; (±)-**1e**, 58072-89-2; (±)-**1f**, 7346-09-0; (±)-**2**, 97948-92-0; (±)-**2** (8-amine), 97948-93-1; (±)-**3**, 97949-55-8; (±)-**3**·$C_4H_4O_4$, 97995-26-1; (±)-**4**, 97889-73-1; (±)-**4**·$C_2H_2O_4$, 97889-74-2; (±)-**5**, 97948-94-2; (±)-**5**·$C_4H_4O_4$, 97995-27-2; (±)-**6a**, 89495-58-9; (+)-**6a**, 89495-59-0; (−)-**6a**, 89495-60-3; (±)-**6b**, 97948-95-3; (±)-**6b**·HCl, 97995-28-3; (±)-**6c**, 89462-04-4; (±)-**6c**·$C_2H_2O_4$, 89426-08-4; (+)-**6c**, 89495-62-5; (−)-**6c**, 89495-63-6; (±)-**6d**, 97948-96-4; (±)-**6d**·HCl, 97995-29-4; (±)-**6e**, 97948-97-5; (±)-**6e**·HBr, 97995-30-7; (±)-**6f**, 97949-07-0; (±)-**6f**·HCl, 97995-31-8; (±)-**7a**, 89495-64-7; (±)-**7a**·$C_2H_2O_4$, 89495-65-8; (+)-**7a**, 89495-66-9; (+)-**7a**·$C_2H_2O_4$, 89495-67-0; (−)-**7a**, 89495-68-1; (−)-**7a**·$C_2H_2O_4$, 89495-69-2; (±)-**7b**, 97949-56-9; (±)-**7b**·HCl, 97995-38-5; (±)-**7c**, 89426-12-0; (±)-**7c**·$C_2H_2O_4$, 89426-13-1; (+)-**7c**, 89495-71-6; (+)-**7c**·$C_2H_2O_4$, 89495-72-7; (−)-**7c**, 89495-73-8; (−)-**7c**·$C_2H_2O_4$, 89495-74-9; (±)-**7d**, 97949-57-0; (±)-**7d**·HCl, 97995-39-6; (±)-**7e**, 97949-58-1; (±)-**7e**·$C_2H_2O_4$, 97995-40-9; (±)-**8**, 71780-67-1; (±)-**8**·$C_4H_4O_4$, 71780-68-2; (+)-**8**, 83434-67-7; (+)-**8**·$C_4H_4O_4$, 89495-75-0; (−)-**8**, 83434-66-6; (−)-**8**·$C_4H_4O_4$, 89495-76-1; (±)-**9**, 72005-59-5; (±)-**9**·$C_4H_4O_4$, 72005-60-8; (±)-**10**, 71780-71-7; (±)-**10**·$C_4H_4O_4$, 71780-72-8; (±)-**11**, 71780-73-9; (±)-**11**·$C_4H_4O_4$, 71780-74-0; (±)-**12**, 97949-00-3; (±)-**12**·1/2$C_4H_4O_4$, 97995-32-9; (±)-**13**, 97949-01-4; (±)-**13**·HCl, 97995-33-0; (±)-**14**, 97949-02-5; (±)-**14**·HCl, 97889-75-3; (±)-**15**, 97949-03-6; (±)-**15**·HCl, 97889-76-4; (±)-**16**, 97949-04-7; (±)-**16**·HCl, 97889-77-5; (±)-**17**, 97889-78-6; (±)-**17**·$C_4H_4O_4$, 97889-79-7; (±)-**18**, 97889-80-0; (±)-**18**·$C_4H_4O_4$, 97889-81-1; (±)-**19**,

71780-69-3; (±)-19·$C_4H_4O_4$, 71780-70-6; (+)-19, 83434-65-5; (+)-19·$C_4H_4O_4$, 89495-77-2; (−)-19, 83434-64-4; (−)-19·$C_4H_4O_4$, 89495-78-3; (±)-20, 71780-77-3; (±)-20·$C_4H_4O_4$, 71780-78-4; (±)-21, 71780-75-1; (±)-21·$C_4H_4O_4$, 71780-76-2; (±)-22, 71780-80-8; (±)-22·$C_4H_4O_4$, 71780-81-9; (±)-23, 97949-05-8; (±)-23·$C_4H_4O_4$, 97995-34-1; (±)-24, 97949-06-9; (±)-24·HCl, 97995-35-2; (±)-25, 97889-82-2; (±)-25·$C_4H_4O_4$, 97889-83-3; (±)-26, 97948-98-6; (±)-26·$C_4H_4O_4$, 97948-99-7; CH_3SNa, 5188-07-8; 4-$CH_3SC_6H_4CH_2Cl$, 874-87-3; $(CH_3)_2NCSCl$, 16420-13-6; C_6H_5COCl, 98-88-4; *N*-methyl-3,4-lutidinium iodide, 6283-41-6; (±)-1,2-dihydro-2-[4-(methylthio)benzyl]-1,3,4-trimethylpyridine, 97907-56-7.

Inhibitors of Blood Platelet Aggregation. Effects of Some 1,2-Benzisothiazol-3-ones on Platelet Responsiveness to Adenosine Diphosphate and Collagen

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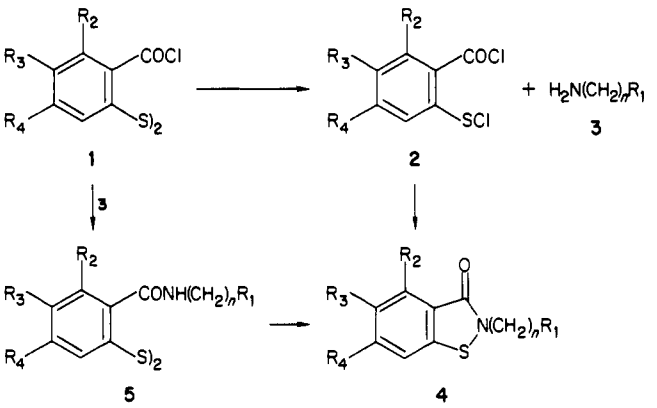
A series of substituted 1,2-benzisothiazol-3-ones was synthesized, and the compounds were tested for ability to inhibit platelet aggregation induced by adenosine diphosphate and collagen in rats and guinea pigs ex vivo. Alkyl substituents at the 2-position bearing a basic group were necessary for ex vivo activity. Several of the compounds were potent inhibitors of adenosine diphosphate induced first-phase aggregation, but adverse toxicological findings terminated their further development. Preliminary studies suggested that inhibition of aggregation was not attributable to inhibition of prostanoid synthesis or to raised levels of cyclic 3′,5′-adenosine monophosphate.

Activation of blood platelets is the first step in hemostasis, the aggregation of platelets stemming blood flow initially and then serving as a nidus for fibrin deposition and permanent closure of the wound[1]. This same sequence of events within vessels probably causes thrombosis, and, hence, one rational approach in the search for antithrombotic drugs is to look for inhibitors of platelet aggregation. Certainly much effort has been spent in this direction since the introduction of a simple photometric method of measuring platelet aggregation[2]. When applied to human citrated platelet-rich plasma (PRP), the technique shows adenosine diphosphate (ADP) to induce aggregation in two phases. The second phase is readily inhibited by nonsteroidal antiinflammatory drugs such as aspirin when tested in vitro[3] or ex vivo[4]. The first phase of aggregation, however, has proved more resistant to therapeutic manipulation. Although there has been some success in the use of aspirin as an antithrombotic agent,[5,6] it could be argued that an inhibitor of first-phase or primary aggregation may have greater potential in the prevention and treatment of platelet-initiated thrombotic events. This proposition is supported by the increasingly wide application[7] of epoprostenol (prostacyclin), a potent inhibitor of primary aggregation induced by a range of aggregating agents in vitro.[8]

Here we report studies on a series of 1,2-benzisothiazol-3-ones, directed toward the selection of potential clinical candidates, the goal being a drug that inhibits first-phase aggregation ex vivo in man and hence a potential antithrombotic agent. When this study was well advanced,[9] a patent application disclosed similar work by another group.[10]

Chemistry. The 1,2-benzisothiazol-3-ones (**4**; Table I) were prepared by a number of methods, most well reported in the literature[11,12] (Scheme I). Reaction of diazotized anthranilic acids with potassium ethyl xanthate followed by hydrolysis and oxidation gave 2,2′-dithiosalicylic acids,[13] which were converted into **1** with thionyl chloride. Some amines of type **3** were commercially available; otherwise

Scheme I



they were synthesized by lithium aluminium hydride reduction of the corresponding nitriles.[14]

The yields in the reactions between **2** and **3**[15] were only moderate but satisfactory for this study. No obvious side

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