aminomethanol products were prepared after the method of Atkinson and Puttick.[15] The epoxide was dissolved in a volume of dry dimethylformamide equal to approximately three times its weight, and 2 equiv of di-*n*-butylamine was added. The reaction was heated to 100–110°, stoppered, and allowed to stir at this temperature for 10–12 hr. The reaction mixture was then steam distilled until about 700 ml of water had been collected. The crude product was collected by extracting the pot residue with ether, drying the extracts ($MgSO_4$), and removing the solvent ether on a rotary evaporator. The products thus attained all gave satisfactory C and H analyses without further purification. Table I lists the reaction conditions and product yields. The products were generally obtained as light-colored waxes with very indistinct melting points.

Antimalarial Testing. The 4-quinolinemethanols were primarily evaluated in blood-induced *Plasmodium berghei* infections of mice. Assessment of activity was on the basis of influence of various doses of the compounds upon the survival times of groups of five mice in comparison with untreated controls (mean survival time 6.2 days). Those surviving more than 60 days were adjudged "cured." Table II shows the comparative data on compounds **6a**, **6b**, **6d**, **6e**, and **6f**; **6c** was inactive at doses to 640 mg/kg. From the background available, antimalarial activity was greatest in **6b**, **6d**, and **6e**, of which **6e** was best. That gave evidence of the worth of the 8-CF_3 grouping in enhancement of antimalarial activity among this series of 2-substituted 4-quinolinemethanols. Some of the intermediates (as, **1a**, **4a**, **13e**, **14e**) were also tested against the murine malaria; all were inactive.

Compounds **6a** and **6b** were evaluated against blood-induced *Plasmodium gallinaceum* infections in chicks.[33] Both were inactive. Patterns of activity in this series were not adequate to justify expanded testing or further extension of the present group.††

References

(1) R. E. Lutz, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freek, G. H. Harnest, N. H. Leake, T. A. Martin, R. J. Rowlett, Jr., J. M. Salsbury, N. H. Shearer, Jr., J. D. Smith, and J. W. Wilson, III, *J. Amer. Chem. Soc.*, 68, 1813 (1946).
(2) J. Mead and J. B. Koepfli, *J. Biol. Chem.*, 154, 507 (1944).
(3) J. P. Schaefer, K. S. Kulkarni, R. Costin, J. Higgins, and L. M. Honig, *J. Heterocycl. Chem.*, 7, 607 (1970).
(4) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, 11, 273 (1968).
(5) W. Pfitzinger, *J. Prakt. Chem.*, 33, 100 (1886).
(6) R. F. Brown, T. L. Jacobs, S. Winstein, M. C. Kloetzel, E. C. Spaeth, W. H. Florsheim, J. H. Robson, E. F. Levy, G. M. Bryan, A. B. Magnusson, S. J. Miller, M. L. Ott, and J. A. Terek, *J. Amer. Chem. Soc.*, 68, 2705 (1946).
(7) M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *ibid.*, 68, 2697 (1946).
(8) A. J. Suggiomo, K. Kato, and T. Kaiya, *J. Med. Chem.*, 11, 277 (1968).
(9) P. E. Thompson and L. M. Werbel, "Antimalarial Agents, Chemistry and Pharmacology," Academic Press, New York, N. Y., 1972, Chapter 8.
(10) J. S. Gillespie, Jr., R. J. Rowlett, Jr., and R. E. Davis, *J. Med. Chem.*, 11, 425 (1968).
(11) J. B. Wommack, Jr., and D. E. Pearson, *ibid.*, 13, 383 (1970).
(12) I. G. Fels, *ibid.*, 11, 887 (1968).
(13) W. E. Rothe and D. P. Jacobus, *ibid.*, 11, 366 (1968).
(14) E. R. Atkinson and A. J. Puttick, *ibid.*, 13, 537 (1970).
(15) E. R. Atkinson and A. J. Puttick, *ibid.*, 11, 1223 (1968).
(16) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, 14, 926 (1971).
(17) S. D. Lesesne and H. R. Henze, *J. Amer. Chem. Soc.*, 64, 1897 (1942).
(18) J. F. Mead, A. E. Senear, and J. B. Koepfli, *ibid.*, 68, 2708 (1946).
(19) P. M. Maginnity and C. A. Gaulin, *ibid.*, 73, 3579 (1951).
(20) K. D. Kulkarni and R. C. Shah, *J. Indian Chem. Soc.*, 26, 171 (1949).
(21) R. C. Shah and V. R. Heeramaneck, *J. Chem. Soc.*, 428 (1936).
(22) G. A. Wiley, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, 86, 964 (1964).
(23) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *ibid.*, **92**, 2377 (1970).
(24) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, 64, 277 (1964).
(25) C. E. Kaslow and M. M. Marsh, *J. Org. Chem.*, 12, 456 (1947).
(26) D. V. R. Goldring and A. E. Senear, *ibid.*, 12, 293 (1947).
(27) R. M. Pinder and A. Burger, *J. Med. Chem.*, 11, 267 (1969).
(28) S. A. Kulkarni and R. C. Shah, *J. Indian Chem. Soc.*, 27, 111 (1950).
(29) G. A. Reynolds and C. R. Hauser, *Org. Syn.*, 30, 70 (1950).
(30) H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, 62, 446 (1940).
(31) H. Gilman and S. M. Spatz, *ibid.*, 63, 1553 (1941).
(32) L. Friedman and H. Schechter, *J. Org. Chem.*, 26, 2522 (1961).
(33) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

††We acknowledge with thanks the assistance of Dr. Edgar A. Steck in the concise presentation of the antimalarial testing data.

Quinazolines and 1,4-Benzodiazepines. 58.[1] The Azido Group, a Novel Pharmacophoric Substituent. 7-Azido-5-phenyl-1,4-benzodiazepines

Robert Y. Ning,* Leo H. Sternbach,

Chemical Research Department

William Pool, and Lowell O. Randall

Pharmacology Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received March 14, 1973*

Some 7-azido-5-phenyl-1,4-benzodiazepines have been prepared. They showed, in animals, potent sedative and anticonvulsant properties. Analogs containing 7-(3,4,5-triazatricyclo[5.2.1.0]dec-4-en-3-yl), 7-(1*H*-tetrazol-5-yl), and 7-(1- and 2-methyltetrazol-5-yl) substituents (**10**, **11**, **12**, and **13**) were found to be inactive.

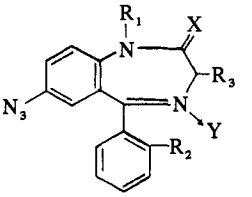
Substituents in the 7 position of the 1,4-benzodiazepine nucleus are known to have a paramount effect on the biological activity of these compounds.[2] In the search for novel substituents which might impart unusual pharmacological properties, we synthesized and studied 7-azido and related 1,4-benzodiazepines.†

We found that an azido (N_3) group in the 7 position of 5-phenyl-1,4-benzodiazepines imparted high pharmacological activity which compares favorably with that exhibited by the corresponding 7-halo and 7-nitro analogs and is vastly superior to that of the corresponding amino compounds. We wish to report on the preparation of these 7-azido compounds (Table I) along with compounds **10–13** which contain a triazole or tetrazole substituent in the 7 position.

Chemistry. The 7-azido group was introduced by di-

†This is, to our knowledge, the first case in which the effect of an azido group on the CNS activity of a drug molecule was studied.

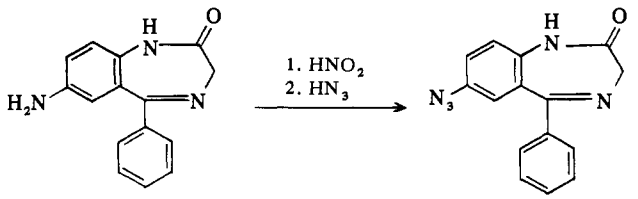
Table I



	X	Y	R_1	R_3	R_2	Method of prepn[a]	Mp, °C	Recrystn solvent[b]	Yield, %	Formula[c]
1	O		H	H	H	A	174-175 dec	I	50	$C_{15}H_{11}N_5O$
2	O		H	H	CF_3	A	178-179 dec	I	67	$C_{16}H_{10}F_3N_5O$[d]
3	O		H	H	Cl	A	186-187 dec	I	70	$C_{15}H_{10}ClN_5O$[d]
4	H_2		CH_3	H	H	A	80-82	II	42	$C_{16}H_{15}N_5$
5	O		H	OH	H	A	188-190 dec	III	65	$C_{15}H_{11}N_5O_2$
6	O		CH_3	H	H	B	123-125 dec	IV	46	$C_{16}H_{13}N_5O$
7	O	O	H	H	H	A	186-188 dec	III	83	$C_{15}H_{11}N_5O_2$
8	O		CH_3	H	F	A	97-99 dec	V	44	$C_{16}H_{12}FN_5O$
9	O		CH_2CH_2OH	H	H	B	158-159 dec	VI	20	$C_{17}H_{15}N_5O_2$

[a] A, prepared from the corresponding 7-amino precursor; B, prepared from 1 by alkylation in the 1 position. [b] I, CH_2Cl_2-hexane; II, petroleum ether (bp 60-90°); III, THF-hexane; IV, Me_2CO-hexane; V, EtOAc-heptane; VI, C_6H_6-hexane. [c] Correct analyses for C, H, and N were obtained for all compounds except for those noted under *d*. [d] Compound 2: C, calcd 55.66; found 55.08. Compound 3: N, calcd 22.46; found 21.58.

azotization of the corresponding 7-amino compounds‡ followed by treatment with hydrazoic acid[3] as illustrated for compound **1**. The 7-azido compounds **1-5**, **7**, and **8**

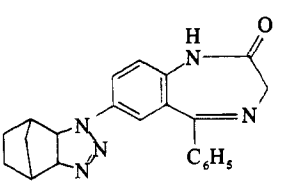


14 1

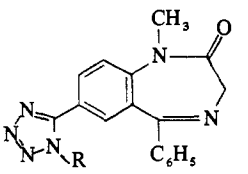
(Table I) were thus obtained from the corresponding 7-aminobenzodiazepines in fair to good yields.§ The 7-azido-1*H*-lactam **1** was alkylated in the 1 position using sodium hydride and alkyl halides to give the 1-methyl (**6**) and the 1-hydroxyethyl (**9**) derivatives.

All the azides reported here showed the strong characteristic infrared absorption band in the region of 2050-2150 cm^{-1} and are sensitive to heat and strong light. Heating above 50° was avoided during recrystallizations, and the compounds were stored in brown bottles. The 7-amino precursors of **1-4** are known. The amino precursors of **5**, **7**, and **8** were prepared by conventional methods which are described in the Experimental Section.

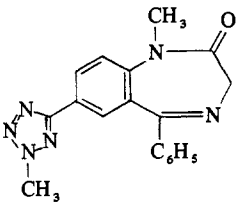
When **1** was allowed to stand in solution with bicyclo[2.2.1]hep-2-ene at room temperature, the anticipated[3] cycloaddition product **10** was obtained in 87% yield. Reaction of 7-cyano-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[4] with ammonium azide in dimethylformamide[5] afforded in 82% yield the corresponding 7-(1*H*-tetrazol-5-yl) derivative **11**. In order to remove the highly acidic tetrazole hydrogen,[6,#] compound **11** was methylated with methyl iodide in the presence of triethylamine. Two monomethyl derivatives were obtained in yields of 46 and 8%. In analogy to the course of the monoalkylation of 5-phenyltetrazole, we assumed that the



10



11, R = H
13, R = CH_3



12

major reaction product had the methyl group in the 2 position[7-9] of the tetrazole ring. Hence, without strict proof, this compound was assigned structure **12** and the other isomer was considered to have structure **13**.

Biological Activity.** All the azides **1-9** were found to be active when screened for sedative, muscle relaxant, taming, and anticonvulsant effects in mice and for sedative and muscle relaxant effects in cats. Methods used in these tests have been described in earlier publications.[2b,10] The results are listed in Table II along with the data for diazepam and chlordiazepoxide. Compounds **1**, **5**, **6**, **8**, and **9** are comparable to diazepam and chlordiazepoxide in their activity. The 7-heterocyclic-substituted compounds **10**, **11**, **12**, and **13** were all found to be inactive.

Experimental Section

Although no spectral data are included in this report, all structural assignments were unambiguously confirmed by ir, supplemented by nmr or uv spectroscopy when necessary.

All melting points were taken in a Thomas-Hoover melting point apparatus and are corrected. All solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure at a bath temperature of 30-50° unless otherwise specified.

The progress of reactions was routinely followed by tlc. All analytical samples were tlc pure. In all cases phosphorescent silica gel

‡ The 7-amino derivatives show a very low biological activity.

§ The yields were not optimized and are in many cases based only on a single experiment.

We have observed that acidic groups attached to the 7 position have a detrimental effect on the pharmacological activity.

** We are grateful to Ms. B. Kappell and Ms. D. Hane for the pharmacological data.

Table II

Compd	Muscle relaxant and taming activity (mice), ED_{50}, mg/kg po: Inclined screen	Muscle relaxant and taming activity (mice), ED_{50}, mg/kg po: Fighting	Behavior (cat), MED, mg/kg po	Anticonvulsant activity (mice), ED_{50}, mg/kg po: Antipentylene-tetrazole	Anticonvulsant activity (mice), ED_{50}, mg/kg po: Antimax shock	Anticonvulsant activity (mice), ED_{50}, mg/kg po: Antimin shock
1	15	15	1.2	4.5	8	40
2	200	25	2	2.6	11	400
3	350	10	0.25	1.1	20	200–400
4	125	25	>10	6.5	45	>400
5	50	12.5	2			
6	20	2.5	5	2.8	12	>>20
7	250	25	10	8.9	48	>800
8	20	2.5	1	0.9	8	>20
9	20	3.1	>1	3.2	11	>20
10	>500			>800	>800	
11	>500	>100		>800	>800	
12	>500	>100				
13	>500	>100				
14[a]	>500	>100	>20	>800	>800	
Diazepam	30	10	0.2	1.4	6.4	64
Chlordiazepoxide	100	40	2	8	30	92

[a] 7-Amino precursor of compound 1.

plates were used. Eluents were chosen from the following group of solvents: C_6H_6; 10% Et_2O in C_6H_6; Et_2O; EtOAc; EtOH–EtOAc (1:1). The developed plates were viewed under uv light.

The following 7-aminobenzodiazepines used as starting materials for the corresponding 7-azido compounds are known: 7-amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one,[11] 7-amino-1,3-dihydro-5-(2-trifluoromethylphenyl)-2*H*-1,4-benzodiazepin-2-one,[12] 7-amino-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one,[11] and 7-amino-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine.[13]

7-Amino-1,3-dihyro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one.†† A solution of 2.0 g (6.7 mmol) of 1,3-dihydro-3-hydroxy-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[14] in 125 ml of DMF was hydrogenated under 1 atm of H_2 using 250 mg of 10% Pd/C as catalyst. Catalyst was removed by filtration and the solvent was evaporated. After recrystallization from CH_3CN, 0.30 g (17%) of the product was obtained, mp >320°. *Anal.* ($C_{15}H_{13}N_3O_2$) C, H, N.

7-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide. A solution of 6.0 g (20.2 mmol) of 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide[11] in 170 ml of THF, containing 200 mg of PtO_2, was hydrogenated at 1 atm for 1 hr. During this time, the product precipitated as it formed. After collection and washing with THF, the crude yield was 4.30 g, mp 267–268° dec. Catalyst was removed from the crude product by solution in hot DMF followed by filtration. Addition of EtOH to the filtrate gave a colorless amorphous solid. After recrystallization from DMF–EtOH, the yield was 3.70 g (69%), mp 274–274.5° dec. *Anal.* ($C_{15}H_{13}N_3O_2$) C, H, N.

7-Amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one. To a fresh solution of 12.53 g (40 mmol) of 1,3-dihydro-5-(2-fluorophenyl)-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one[11] in 80 ml of 6 *N* HCl was added at once, in one portion, a solution of 30.0 g (132 mmol) of $SnCl_2 \cdot 2H_2O$ in 80 ml of 6 *N* HCl. The mixture was stirred vigorously at room temperature for 16 hr and then basified with 50% aqueous KOH to dissolve the tin salts. Crude product was collected and washed thoroughly with H_2O: 11.3 g; mp 204–205° dec. After recrystallizations from THF–hexane, the yield was 7.22 g (64%), mp 202–204° dec. *Anal.* ($C_{16}H_{14}FN_3O$) C, H, N.

General Procedure for the Conversion of 7-Aminobenzodiazepines to the Corresponding 7-Azides (Table I, Compounds 1–5, 7, 8). In a mixture of 2.5 ml of 12 *N* HCl and 60 ml of H_2O was dissolved 10 mmol of the 7-aminobenzodiazepine. The solution was chilled in ice. An ice-cold solution of 759 mg (11 mmol) of $NaNO_2$ in 2.5 ml of H_2O was added with stirring over 3 min. After 10 min at 0°, an ice-cold solution of 715 mg (11 mmol) of NaN_3 in 2.5 ml of H_2O was added in portions. A cream-colored precipitate formed immediately, accompanied by copious evolution of nitrogen. Stirring was continued for 1 hr at 0°. The mixture was made basic (pH 13) with NaOH solution and then extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with H_2O, dried, and evaporated. Crystallizations from the appropriate solvents gave the pure azides. Heating above 50° was avoided during recrystallizations. The melting points, solvents of crystallizations, and yields are summarized in Table I.

7-Azido-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6). To a stirred solution of 1.11 g (4.0 mmol) of the 1-desmethyl azide (1), in 20 ml of molecular sieves–dried THF, was added at room temperature, under nitrogen, 216 mg of a 50% NaH dispersion in oil (4.5 mmol of NaH). Stirring at room temperature was continued for 20 min after the hydrogen evolution had subsided. Methyl iodide (2.84 g, 20 mmol) was injected in one portion. After 1 hr of stirring, salts were removed by filtration. Evaporation of the filtrate gave a gum which was mixed with warm C_6H_6 (40°) and then filtered again to remove some insoluble material. The residue after the evaporation of the C_6H_6 was dissolved in a Me_2CO–hexane mixture. Slow evaporation of this solution in an open beaker gave 6 as yellow prisms: 678 mg; mp 118–120.5° dec. After recrystallizations in the same manner from Me_2CO–hexane, the yield was 535 mg (46%), mp 122.5–124° dec.

7-Azido-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (9). To a stirred solution of 1.39 g (5.0 mmol) of the 1-H azide (1), in 20 ml of molecular sieves–dried THF, was added at room temperature, under nitrogen, 360 mg of a 50% NaH dispersion in oil (7.5 mmol of NaH). About 5 min after hydrogen evolution subsided, 1.25 g (10 mmol) of 2-bromoethanol was injected. After 20 hr of stirring at room temperature, the mixture was poured into 100 ml of H_2O. The mixture isolated by extractions with CH_2Cl_2 was concentrated to a volume of about 5 ml and transferred onto a column of 100 g of silica gel (Grace, 100–200 mesh) packed in anhydrous Et_2O. Elution with 750 ml of anhydrous Et_2O gave recovered starting material which after recrystallizations from C_6H_6–hexane weighed 856 mg (62%), mp 174–175° dec. Further elution with 750 ml of Et_2O gave the product which after recrystallizations from C_6H_6–hexane weighed 148 mg (20% based on unrecovered starting material) as light yellow needles, mp 158–159° dec.

3-(5-Phenyl-1,3-dihydro-2-oxo-2*H*-1,4-benzodiazepin-7-yl)-3,4,5-triazatricyclo[5.2.1.0]dec-4-ene (10). A solution of 2.77 g (10 mmol) of the azide 1 and 3.76 g (40 mmol) of bicyclo[2.2.1]hept-2-ene in 50 ml of CH_2Cl_2 was allowed to stand at 20° for 2 days. Evaporation of the solvent followed by crystallization of the residual gum from EtOAc yielded 3.22 g (87%) of the yellow amorphous adduct, mp 200–201° dec. The melting point remained unchanged and the material stayed amorphous on reprecipitation from EtOAc. It appeared to decompose gradually on further attempts at recrystallization. *Anal.* ($C_{22}H_{21}N_5O$) C, H, N.

1,3-Dihydro-1-methyl-5-phenyl-7-(1*H*-tetrazol-5-yl)-2*H*-1,4-benzodiazepin-2-one (11). A solution of 3.90 g (60 mmol) of NaN_3 and 3.21 g (60 mmol) of NH_4Cl in 35 ml of H_2O was added to a solution of 5.50 g (20 mmol) of 7-cyano-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[4] in 100 ml of DMF. The mixture was heated on a steam bath for 2.5 days. Solvents were evap-

†† This compound was first prepared by A. Stempel, as described. We are grateful to Dr. Stempel for a supply of this compound.

orated at 70–80°. The residual mixture was suspended in 100 ml of H_2O. The suspension was made basic (pH >10) with 50% aqueous KOH and the nonacidic matter removed by two washings with CH_2Cl_2. Acidification of the aqueous layer with HCl to about pH 1, followed by standing for 1 hr, yielded a yellow amorphous solid: 6.33 g, mp 269–271° dec. After recrystallization from DMF–H_2O, 5.20 g (82%) of yellow prisms were obtained, mp 278–280° dec (darkened above 245°). Further recrystallizations did not change the melting point. *Anal.* ($C_{17}H_{14}N_6O$) C, H, N.

1,3-Dihydro-1-methyl-7-(2-methyltetrazol-5-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (12) and 1,3-Dihydro-1-methyl-7-(1-methyltetrazol-5-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (13). To a solution of 318 mg (1.0 mmol) of 11 and 0.154 ml (1.1 mmol) of Et_3N in 5 ml of Me_2CO was added 0.069 ml (1.1 mmol) of CH_3I. The mixture was allowed to stand at 20° under N_2 for 6 hr. The solvent was evaporated and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer containing the nonacidic reaction products (292 mg of gum) was evaporated and the isomeric N-methylated products 12 and 13 (tlc R_f values 0.47 and 0.22, respectively, silica gel, EtOAc) were separated by preparative tlc (three silica gel plates, 20 cm × 20 cm × 1.5 mm; EtOAc as eluent). Pure 12 initially obtained as a gum (206 mg) crystallized from C_6H_6–hexane as light yellow flakes (154 mg; 46%), mp 201–202.5°. *Anal.* ($C_{18}H_{16}N_6O$) C, H, N. Pure 13 also obtained initially as a gum (36 mg) crystallized from C_6H_6–hexane as light yellow needles (28 mg; 8%), mp 212–214°. Larger amounts of 12 and 13 were prepared in similar yields following essentially the same procedure, but using column chromatography (silica gel, EtOAc followed by 5% MeOH in EtOAc as eluents) for the separation of the isomers.

Acknowledgments. We are grateful for the services provided by the following members of our Physical Chemistry Department under the direction of Dr. R. P. W. Scott: Dr. F. Scheidl (elemental analyses), Mr. S. Traiman (ir), Dr. V. Toome (uv), and Dr. T. Williams (nmr).

References

(1) R. I. Fryer, D. L. Coffen, J. V. Earley, and A. Walser, *J. Heterocycl. Chem.*, in press (paper 57).
(2) (a) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, 53, 577 (1964); (b) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous Systems," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, p 247.
(3) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 239, 255.
(4) L. H. Sternbach, G. Saucy, F. A. Smith, M. Müller, and J. Lee, *Helv. Chim. Acta*, 46, 1720 (1963).
(5) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, 80, 3908 (1958).
(6) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, 22, 1142
(7) R. S. Mihina and R. M. Herbst, *ibid.*, 15, 1082 (1950).
(8) R. A. Henry, *J. Amer. Chem. Soc.*, 73, 4470 (1951).
(9) R. Raap and J. Howard, *Can. J. Chem.*, 47, 813 (1969).
(10) L. H. Sternbach, G. A. Archer, J. V. Earley, R. Ian Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, 8, 815 (1965).
(11) L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *ibid.*, 6, 261 (1963).
(12) L. H. Sternbach and G. Saucy, U. S. Patent 3,182,054 (May 4, 1965, example 45).
(13) L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, 28, 3013 (1963).
(14) E. Reeder, A. Stempel, and L. H. Sternbach, Belgium Patent 629,227 (Oct 21, 1963).

N-Substituted 2-Amino-1-(2-thienyl)ethanols as β-Adrenergic Blocking Agents

C. Corral, V. Darias, M. P. Fernández-Tomé, R. Madroñero,* and J. del Río

Department of Medicinal Chemistry, Centro Nacional de Química Orgánica, Madrid-6, Spain. *Received February 20, 1973*

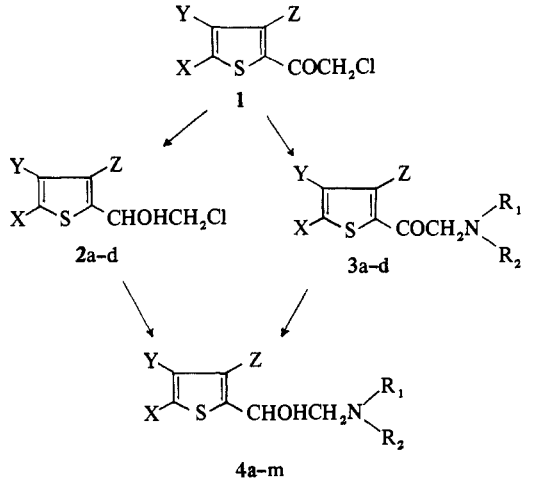
The synthesis and pharmacological properties of a series of N-substituted 2-amino-1-(2-thienyl)ethanols are described. A strong β-adrenergic blocking activity has been observed in *N*-isopropyl- or *N*-*tert*-butyl-substituted ring-chlorinated compounds.

Elucidation of the structure of the neurotransmitters of the sympathetic nervous system, epinephrine and norepinephrine, provided the impetus for extensive molecular modifications of these catecholamines in search of adrenergic stimulant or adrenergic blocking activity. The benzenoid hydroxyl group of the catecholamines has been replaced by a variety of substituents including chlorine,[1] fluorine,[2] iodine,[3] alkyl,[4] nitro,[5] amino,[6] alkoxy,[7] and alkyl- or arylsulfonamide.[8] The 2-hydroxyethylamino side chain and the N substituent have also been modified.[9] It appears, however, that the bioisosteric replacement of the benzene ring by thiophene has not received much attention, in spite of the extensive demonstration of the equivalence of these two rings in many therapeutics fields.[10]

A series of thienylethanolamine derivatives, some of which contain one or two chlorine atoms on the thiophene ring, has been prepared and the pharmacological activity of the new compounds has been tested. Since some of them, especially those with branched *N*-alkyl substituents, seem to fulfill the structural requirements for β-adrenergic blocking activity,[11] this pharmacological property was especially considered in the screening tests.

Chemical Synthesis. All the thienyl ethanolamine derivatives 4 (Table III) reported in this work are racemic modifications and were prepared from the appropriate chloroacetylthiophenes 1 by two alternate routes (Scheme I).

Scheme I



In route A, the chloroacetylthiophene 1 was reduced by the Meerwein-Ponndorf method to the corresponding 2-chloro-1-(2-thienyl)ethanol 2 (Table I) and the latter upon treatment with an amine yielded the corresponding thienylethanolamine derivative 4.

In route B, 1 was allowed to react with an amine and the obtained amino ketone 3 (Table II) was reduced to 4 by $NaBH_4$.