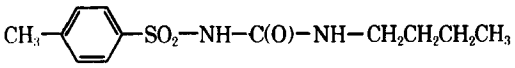
# Synthesis and Pharmacological Evaluation of Some Tosylbiurets and Tosylthiocarbamates as Potential Hypoglycemic Agents

By DOUGLAS C. KRIESEL and JAMES MENZIE*

**The synthesis and preliminary pharmacological screening of some *p*-toluenesulfonylbiurets and alkyl *p*-toluenesulfonylthiocarbamates are described. The biurets were prepared by refluxing tosyl isocyanate with the appropriate urea, and the thiocarbamates were formed by the addition of selected mercaptans to the same isocyanate. None of the tosylbiurets possessed hypoglycemic activity; however, propyl tosylthiocarbamate lowered serum glucose levels in mice to approximately the same extent as tolbutamide.**

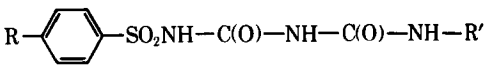
SIGNIFICANT STRIDES in the treatment of diabetes mellitus have been made since the introduction of oral hypoglycemic agents such as the sulfonylureas and the biguanides. In particular, the drug tolbutamide (I) has been successful in the treatment of the maturity-onset form of this disease.



(I)

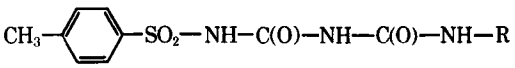
However, there are certain situations where tolbutamide therapy is inadequate; these cases have responded in some instances to other oral hypoglycemic agents. The purpose of this research was to attempt to prepare some hypoglycemic drugs that would be clinically effective in the treatment of diabetes mellitus.

Two types of derivatives of *p*-toluenesulfonyl isocyanate have been made and screened as hypoglycemic agents. Some *p*-toluenesulfonylbiurets were prepared to add to a series of molecules of this type that were previously recorded in the literature (1). These previously synthesized biurets did possess hypoglycemic activity although of a lower order than tolbutamide.



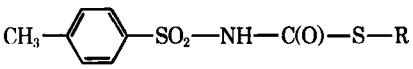
(II) R = $NH_2$, R′ = *n*-butyl
(III) R = $CH_3$, R′ = *n*-butyl
(IV) R = $CH_3$, R′ = 3-methoxy-*n*-propyl

Molecular models have demonstrated that these compounds (II, III, IV) possess a total length of about 2.5 Å. more than the known hypoglycemic agent, tolbutamide. The decrease in hypoglycemic activity might have resulted from the fact that the receptor protein was unable to accommodate for the increase in molecular size offered by the additional two terminal carbon atoms. The synthesis of some closely related tosylbiurets (V, VI, VII, VIII) was carried out to determine whether a steric relationship existed in this series.



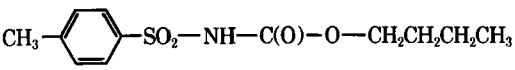
(V) R = H
(VI) R = $CH_3$
(VII) R = $CH_2CH_3$
(VIII) R = $CH_2CH_2CH_3$

A series of tosylthiocarbamates, (IX, X, XI, XII), also prepared from *p*-toluenesulfonyl isocyanate, was synthesized for biological testing.



(IX) R = $CH_3$
(X) R = $CH_2CH_3$
(XI) R = $CH_2CH_2CH_3$
(XII) R = $CH_2CH_2CH_2CH_3$

It was hoped that through substitution of a divalent sulfur atom for its bioisoster, the NH, in the tosylureas, a favorable change could be made which would lead to more useful molecules. A previously reported analog of the above, *n*-butyl *N*-tosylcarbamate (XIII), has been shown to be slightly active in reducing serum glucose levels in fasted rats (2). In this case, substitution of an



(XIII)

ether oxygen, which is also a bioisoster of the NH group, lowered the hypoglycemic activity of the resultant molecule when compared to tolbutamide.

## DISCUSSION

The preparation of the biurets was accomplished by condensing the appropriate urea with tosyl isocyanate. The urea was dissolved in DMSO and added to the isocyanate in benzene to facilitate a homogeneous mixture. Nucleophilic attack by the unsubstituted nitrogen of the urea on the carbonyl of the isocyanate occurred yielding the corresponding tosylbiuret. The question of whether the disubstituted biurets were of the 1,3- or the 1,5- type was answered by obtaining an NMR spectrum for 5-methyl-1-tosylbiuret. A doublet at 2.70 p.p.m. ($CH_3$) and a quadruplet at 7.10 p.p.m. (NH) showed that coupling was taking place between the methyl group and an adjacent proton.

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TABLE I—CHARACTERIZATION OF THE DERIVATIVES OF *p*-TOLUENESULFONYL ISOCYANATE

| Compound | M.p., °C. | Yield, % | Anal.,% Calcd. | Found |
|---|---|---|---|---|
| | | **A. Tosylbiurets** | | |
| V | 183–185 | 45.9 | C, 42.07 | 42.24 |
| | | | H, 4.31 | 4.52 |
| VI | 174–176 | 68.7 | C, 44.28 | 44.27 |
| | | | H, 4.83 | 4.90 |
| | | | N, 15.49 | 15.20 |
| VII | 165–167 | 59.9 | C, 46.32 | 46.57 |
| | | | H, 5.30 | 5.42 |
| | | | N, 14.74 | 14.73 |
| VIII | 112–114 | 37.8 | C, 48.14 | 48.43 |
| | | | H, 5.73 | 5.92 |
| | | **B. Tosylthiocarbamates** | | |
| IX | 132–134 | 57.1 | C, 44.05 | 44.27 |
| | | | H, 4.53 | 4.67 |
| X | 78–80 | 76.9 | C, 46.30 | 46.32 |
| | | | H, 5.06 | 5.19 |
| XI | 80–82 | 40.4 | C, 48.32 | 48.56 |
| | | | H, 5.54 | 5.60 |
| XII | 60–62 | 44.4 | C, 50.14 | 50.38 |
| | | | H, 5.97 | 5.98 |

TABLE II—SERUM GLUCOSE LEVELS OF SOME DERIVATIVES OF *p*-TOLUENESULFONYL ISOCYANATE

| | Mean Serum Glucose Level, mg.% ± *SD* |
|---|---|
| **Tosylbiurets** | |
| Control (0.1 ml. propylene glycol) | 130 ± 32 |
| Tolbutamide, 25 mg./kg. | 70 ± 12 |
| V, 25 mg./kg. | 160 ± 13 |
| VI, 25 mg./kg. | 182 ± 11 |
| VII, 25 mg./kg. | 132 ± 16 |
| VIII, 25 mg./kg. | 118 ± 15 |
| **Tosylthiocarbamates** | |
| Control (0.1 ml. of 5% acacia) | 115 ± 22 |
| Tolbutamide, 25 mg./kg. | 80 ± 19 |
| IX, 25 mg./kg. | 109 ± 23 |
| X, 25 mg./kg. | 114 ± 22 |
| XI, 25 mg./kg. | 83 ± 22 |
| XII, 25 mg./kg. | 110 ± 34 |

When $D_2O$ was added, the methyl peak appeared as a singlet and the peak at 7.10 p.p.m. disappeared. This could only occur with the 1,5-disubstituted analogs.

Formation of the tosylthiocarbamates readily took place at room temperature when the thiol was added to tosyl isocyanate in the presence of a few drops of the catalyst, pyridine. Crystallization of the appropriate product was accomplished when the mixture in benzene was cooled to 10° and previously cooled cyclohexane was slowly added to reach the cloud point.

## EXPERIMENTAL

All melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. All of the elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

**Tosylbiurets**—*p*-Toluenesulfonyl isocyanate[1] (3.0 g., 0.015 mole) was dissolved in 30 ml. of dry benzene and added to a solution of the appropriate urea (0.015 mole) previously dissolved in 10 ml. of dimethyl sulfoxide. The mixture was refluxed for 48 hr. and the solution was then concentrated *in vacuo* to a viscous oil. The oil was dissolved in 15 ml. of ethanol and water was added to the cloud point. Cooling in ice water and scratching the sides of the vessel yielded a white crystalline product that was recrystallized from aqueous ethanol (Table I).

**Tosylthiocarbamates**—*p*-Toluenesulfonyl isocyanate (5.0 g., 0.025 mole) was quickly dissolved in 20 ml. of dry benzene and the appropriate mercaptan (0.025 mole) was added along with two drops of pyridine. The mixture was let stand at room temperature for 24 hr. and then cooled to 10°. Cyclohexane previously cooled to the same temperature was added slowly to reach the cloud point and after briefly scratching the sides of the vessel, the mixture was kept at 10° until crystallization ensued. Recrystallization of the white crystalline solid took place from a mixture of benzene–cyclohexane (Table I).

## PHARMACOLOGICAL DATA

Screening for reduction of serum glucose levels was carried out using the Beckman Ultramicro adaptation of the method of Keston and Teller (3). This method involves a coupled enzyme system and utilizes glucose-oxidase-peroxidase and the chromogen, *o*-dianisidine. Initially, the oxidase converts glucose to gluconic acid and hydrogen peroxide; then the $H_2O_2$ formed is transformed to oxygen by the peroxidase. Finally the oxygen reacts with the chromogen to form a stable color complex which is read spectrophotometrically at 410 mμ. The intensity of the color formed is proportional to the glucose concentration.

The tosylbiurets were screened using mixed white rats that had been fasted for 24 hr. The compound was dissolved in propylene glycol and administered intraperitoneally (approximately 0.1 ml. was given). After 1 hr. a sample of blood was obtained by excising a portion of the tail, after which the sample was quickly centrifuged to obtain the necessary amount of serum.

[1] Purchased from Aldrich Chemial Co. Milwaukee, Wisc.

Fasted mixed white mice were used to screen the tosylthiocarbamates for hypoglycemic activity. The compounds were suspended in 5% acacia and administered intraperitoneally in a dose of 0.1 ml. After 1 hr., a sample of blood was obtained by decapitation and after immediate centrifuging, a serum sample was collected.

No hypoglycemic activity was obtained in the tosylbiuret series signifying that these molecules do not accommodate well with the receptor sites necessary to initiate the release of endogenous insulin.

*n*-Propyl *N*-tosylthiocarbamate was shown to be approximately as active as tolbutamide when tested in mice according to the enzymatic method described in this communication.

REFERENCES

(1) Haack, E., *Arzneimittel-Forsch.*, **8**, 444(1958)

(2) McLamore, W. M., Fanelli, G. M., P'an, S. Y., and Laubach, G. D., *Ann. N. Y. Acad. Sci.* **74**, 443(1959).

(3) Beckman Ultramicro Analytical System Instruction Manual UM-IM-2, Technical Bulletin No. 6073D

*Keyphrases*

Tosylbiurets, thiocarbamates—synthesis

Propyl tosylthiocarbamate—hypoglycemic activity

Colorimetric analysis—spectrophotometer

# Antiradiation Compounds XII. Dithiocarbamates of Strongly Basic Acridines and Quinaldines

By WILLIAM O. FOYE, DOUGLAS H. KAY, and PRAMOD R. AMIN*

**Dithiocarbamates of strong heterocyclic bases (pKa 8–12) in the acridine and quinaldine series have been obtained, with further examples of the formation of imino-*N*-carbodithioates. Significant radiation protection of mice was found for the dithiocarbamate ester of 9-aminoacridine, whereas dithiocarbamates of both stronger and weaker bases were nonprotective.**

Significant radiation protection in mice irradiated with 1000 r ($\gamma$-rays) has been found for the dithiocarbamate of a strongly basic heterocyclic imine (1). The base was 1,2-dihydro-1-methyl-2-iminopyridine, obtained by ring-*N*-alkylation of 2-aminopyridine, and has a pKa of 12.2. Dithiocarbamates of the corresponding 4-iminopyridine and 2-iminopyrimidine gave no radiation protection at this radiation level, however. In order to determine structural requirements for radiation protection by dithiocarbamates of strongly basic heterocycles, preparation of dithiocarbamates of this type of compound has been extended to include acridines and quinaldines.

Dithiocarbamates were generally prepared from these bases, for which pKa values ranged from 8–12 (2) in alcohol with or without the presence of additional base such as pyridine or triethylamine. The dithiocarbamates were obtained as esters, salts of the heterocyclic base, or salts of the added base; the nature of the product was unpredictable. Characteristic absorption for dithiocarbamates was observed in the UV at 220, 240–250, 260–275, and 290–310 m$\mu$ (3) and in the IR near 1,000 cm.$^{-1}$ (1) for these products, providing further evidence for dithiocarbamate formation of imines. In contrast to dithiocarbamate formation of aliphatic amines which generally takes place quite rapidly (4), some of the products reported here required a number of days to form.

Radiation protection in mice was found for the dithiocarbamate of 9-aminoacridine (pKa = 10.0) *versus* 825 r (X-rays). No protection was reported for several other members of these series made from heterocycles having either greater or lesser basicities.

## DISCUSSION

The method of Albert (5) was used to prepare 3-aminoacridine (pKa = 8.0). Treatment of this compound with carbon disulfide in ethanol gave an undefinable product, but in the presence of a large excess of triethylamine, the triethylammonium salt of 3-acridyldithiocarbamate was obtained. In contrast to this behavior, 9-aminoacridine (pKa = 10.0) was converted to ethyl 9-acridyldithiocarbamate when treated with carbon disulfide in ethanol in either the presence or absence of triethylamine. The yield was larger in the former case, however. The UV absorption spectrum in ethanol showed peaks at 243 and 270 m$\mu$ for the 3-isomer and 261 and 304 m$\mu$ for the 9-isomer.

The procedure of Albert (6) was used to prepare 9-imino-10-methylacridinium iodide (pKa = 11.1). This compound was treated with sodium hydroxide to yield 9-amino-9-hydroxy-10-methylacridine which was dehydrated to yield 9,10-dihydro-9-imino-10-methylacridine. Both the hydroxy and the de-

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* In part.