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α-SUBSTITUTED SULFONAMIDES. II[1]. α-NITROSO (OXIMINO) DERIVATIVES

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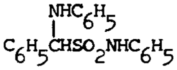
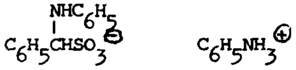
The literature contains many references to modified α-aminoacids which have been synthesized and examined for enzyme inhibitory activity in the search for potential antitumor and antihypertensive agents. Models show that α-aminosulfonamides would be isosteric with α-aminoacids, but an authentic synthesis of such compounds has thus far not been reported. One supposed synthesis of α-aminosulfonamides appears in the literature[2]; however, it has since been shown[3] that these compounds, originally assigned the structure Ia, in fact have the amine salt structure (Ib).



$$\begin{array}{l} \quad NHC_6H_5 \\ \quad | \\ C_6H_5CHSO_2NHC_6H_5 \end{array}$$

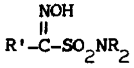
Ia



$$\begin{array}{l} \quad NHC_6H_5 \\ \quad | \\ C_6H_5CHSO_3^{\ominus} \end{array} \qquad C_6H_5NH_3^{\oplus}$$

Ib

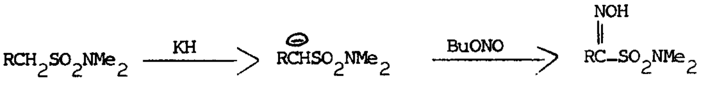
In the course of our efforts to prepare α-aminosulfonamides, we isolated the first example of a new functional system, the α-oximinosulfonamides, II.



$$\begin{array}{l} \quad\; NOH \\ \quad\;\; \| \\ R'\text{-}C\text{-}SO_2NR_2 \end{array}$$

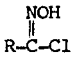
II

Reduction of the recently reported α-nitrosulfonamides[1] by catalytic, chemical, and electrolytic means was investigated, and the products were many and complex. From the electrolytic reduction was isolated, in small amounts, the α-oximinosulfonamide II (R'=C_6H_5, R=Me). A suitable preparative method was then developed, involving the reaction of the α-carbanion of a sulfonamide (prepared using potassium hydride in THF) with a nitrite ester. Compounds IIa (m.p. 156-57°, 76% yield), IIb (m.p. 92-93.5°, 40% yield), and IIc (m.p. 92-93°, 50% yield)[4] were prepared in this way. The assigned structures were confirmed by infrared and NMR spectra. The α-oximino sulfonamides may be considered to be either derivatives of the (unknown) α-ketosulfonamides or related to the hydroximyl structures (III).



$$RCH_2SO_2NMe_2 \xrightarrow{KH} R\overset{\ominus}{C}HSO_2NMe_2 \xrightarrow{BuONO} R\overset{\overset{NOH}{\|}}{C}-SO_2NMe_2$$

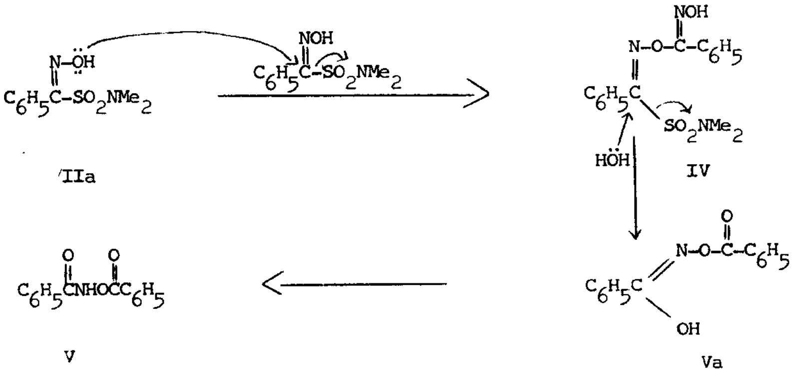
II



III

a, R = C_6H_5-
b, R = $C_6H_5CH_2CH_2$-
c, R = CH_3

II does not give a color with ferric chloride reagent, and is stable in dilute aqueous base and ethanolic hydrazine; it is sensitive to acid, particularly on warming. Under such conditions IIa gave benzoic acid, benzonitrile, and benzamide. In addition, a small amount of N,O-dibenzoylhydroxylamine (V[5]) was obtained from hot formic acid. The formation of V can be rationalized by the attack of the nucleophilic oxime oxygen of IIa on the electrophilic center of another molecule of IIa to give IV; this is hydrolyzed (prolonged exposure to dil. HCOOH) to Va, which is tautomeric with V.



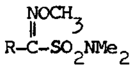
IIa

IV

V

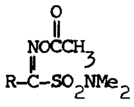
Va

The oximes can be O-alkylated in aqueous alkaline solution to give the compounds VIa



$\mathrm{R{-}\overset{NOCH_3}{\overset{\|}{C}}{-}SO_2NMe_2}$

VI



$\mathrm{R{-}\overset{NO\overset{O}{\overset{\|}{C}}CH_3}{\overset{\|}{C}}{-}SO_2NMe_2}$

VII

a, R = C_6H_5-
b, R = $C_6H_5CH_2CH_2$-
c, R = CH_3

[m.p. 47-49°, 73% yield], VIb [b.p. 119-20(0.5), 70% yield], and VIc [b.p. 59-61(0.1), 52% yield], and acylated in refluxing acetic anhydride to give VIIa [m.p. 104-105°, 65% yield], and VIIb [m.p. 97-99°, 65% yield].

The O-methyl ether (VIa) proved resistant to attempted reduction with diborane[6] or to reaction with methyl Grignard reagent.

REFERENCES

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2. L. Neelakantan and W. H. Hartung, *J. Org. Chem.* **24**, 1943 (1959).
3. Independently by the present authors, and by R. G. Bass, J. D. Smith, and J. Andrako, Abstracts, 16th Annual Southeastern Regional Meeting of the American Chemical Society, Charleston, West Virginia, October 1964, No. 134.
4. Caution should be exercised in exposing these compounds to heat. Purification of a crude sample of IIc by distillation resulted in a violent explosion.
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