(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.
(8) All melting points were measured on a micro hot plate, and are not corrected. The ^{1}H NMR spectra were recorded with a JEOL 100-MHz spectrometer in parts per million (δ) in $CDCl_3$ solution with Me_4Si as an internal standard. The ir spectra were obtained with a Unicam Sp 200 spectrophotometer. All the reactions were controlled by thin layer chromatography. The uv spectra were measured in 95% EtOH. The microanalyses were performed in our microanalytical laboratory (head Z. Celler, M.S.). Specific rotations were determined on a Perkin-Elmer 141 polarimeter.

Stereochemistry of Bockmühl's Synthesis of Methadone

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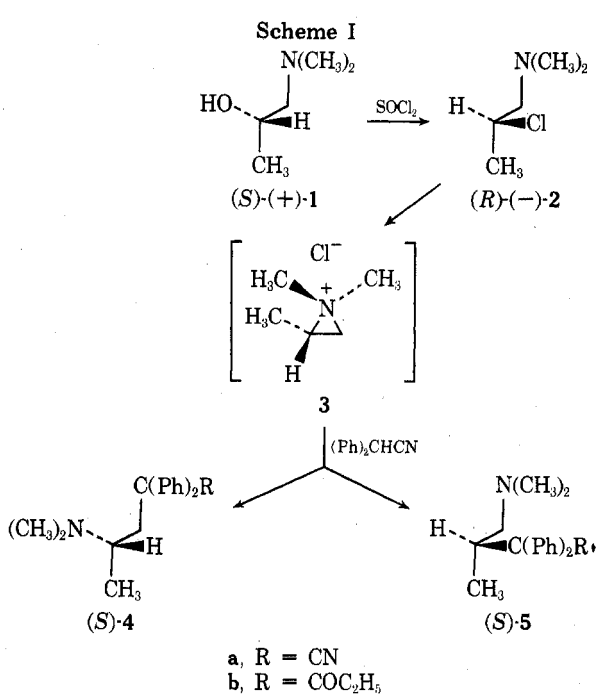
Methadone (**4b**) was first prepared in racemic form by Bockmühl and Erhardt[1] according to the approach outlined in Scheme I. The chloro amine **2** obtained from chlorination of (±)-1-dimethylamino-2-propanol (**1**) with thionyl chloride was treated with sodium diphenylacetonitrile to give a mixture of aminonitriles **4a** and **5a**. The aziridinium ion intermediate **3** has been proposed to account for the rearranged product **4a**.[2] Grignard reaction of **4a** with ethylmagnesium bromide followed by acid hydrolysis afforded methadone (**4b**). Similar treatment of **5a** gave rise to isomethadone (**5b**). More recently, amino alcohol (+)-**1** has been obtained from ethyl L-(−)-lactate (aminolysis, reduction) and thus assigned the (*S*)-(+) configuration.[3] The absolute configurations (shown in Scheme I) of the aminonitriles **4a**[4] and **5a**[5] and thus methadone and isomethadone have also been established. We have found that the conversion of **1** to **4a** and **5a** via **2** is stereospecific and proceeds with the stereochemistry as depicted in Scheme I.

Treatment of (*S*)-(+)-**1** with thionyl chloride in chloroform by the method of Schultz and Sprague[2] afforded (−)-1-dimethylamino-2-chloropropane (**2**) hydrochloride, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), which was converted to the free base, $[\alpha]^{25}D$ −43.9° (*c* 2.55, $CHCl_3$), and treated with sodium diphenylacetonitrile in toluene essentially by the original procedure.[1] The mixture of aminonitriles thus obtained was separated by preparative thin layer chromatography on silica gel, affording substantially optically pure (*S*)-(+) ≡ L-(+)-**4a** and (*S*)-(+) ≡ D-(+)-**5a** by comparison of optical rotations with the literature values (see Experimental Section).

Scheme I



a, R = CN
b, R = COC_2H_5

The opposite configurations and identical optical purity of the nitriles **4a** and **5a** constitute compelling evidence that the aziridinium ion pathway is the exclusive mode of product formation in the alkylation step. It follows that unrearranged **5a** was formed with net retention of configuration (double inversion) while **4a** has the inverted configuration since the opening of the aziridinium ion **3** at the unsubstituted carbon would not alter the asymmetric center.[6] Thus the chloride **2** must have the (*R*)-(−) configuration and must have been obtained from **1** with inversion.

The present results clearly exclude the formation of an intermediate aziridine during chlorination of **1** and are best rationalized by SN2 displacement of the chlorosulfite ester of **1** hydrochloride. The high local concentration of chloride ion enforced by the internal ammonium ion of **1** should enhance the SN2 displacement process and may have been a factor in the high degree of stereospecificity observed in this case.[7]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured on a Rudolph polarimeter having a readability of ±0.01°, using a 1-dm tube. ^{1}H NMR spectra were obtained with Varian A-60 and T-60 instruments.

(−)-1-Dimethylamino-2-chloropropane Hydrochloride (2). To a solution of 3.77 g (0.0366 mol) of (*S*)-(+)-1-dimethylamino-2-propanol (**1**),[3] $[\alpha]^{25}D$ +24° (*c* 2.17, EtOH), in 10 ml of chloroform stirred and cooled in an ice–salt bath was slowly added 5.72 g (0.048 mol) of freshly distilled thionyl chloride in 2 ml of chloroform. When addition was complete a precipitate formed. The flask was allowed to warm to room temperature over 30 min, then heated to reflux for 30 min. The precipitated material redissolved on heating but the product crystallized from the boiling solvent shortly thereafter. The cooled mixture was diluted with ether and filtered. The crude product, 5.5 g (95%), was recrystallized from 2-propanol, giving 3.73 g (64%) of (−)-1-dimethylamino-2-chloropropane hydrochloride (**2**), mp 192–193°, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O) [lit.[2] mp for (±) hydrochloride 185–186°].

(−)-1-Dimethylamino-2-chloropropane (2). To a solution of 2.2 g of (−)-**2** hydrochloride in an equal volume of water was added 1.5 ml of 20% sodium hydroxide solution until the mixture was distinctly alkaline to pH paper. The free amine was extracted with two 5-ml portions of ether. The combined ether layers were dried over anhydrous potassium carbonate and distilled to give 0.8 g of (−)-1-dimethylamino-2-chloropropane (**2**): bp 115° [lit.[2] bp for (±) 62–63° (100–110 mmHg)]; $[\alpha]^{25}D$ −43.9° (*c* 2.55 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3, J = 6 Hz, CCH_3), 2.28 (s, 6, NCH_3), 2.50 (m, 2), 4.07 (m, 1), identical with an authentic racemic sample.

Alkylation of Diphenylacetonitrile with (−)-2. A 1.0-g sample of the hydrochloride salt of (−)-**2**, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), was converted to the base as previously described and treated with sodium diphenylacetonitrile by the Bockmühl procedure.[1] A 0.52-g portion of the crude mixture of aminonitriles was separated by preparative thin layer chromatography (silica gel, E. Merck, benzene–methanol 8:2) affording 145.7 mg of (*S*)-(+)-**4a**, recrystallized from petroleum ether, mp 100–101°, $[\alpha]^{25}D$ +49° (*c* 0.68, absolute EtOH) [lit.[8] mp 100–101°, $[\alpha]^{25}D$ +50° (*c* 1.5, absolute EtOH)], and 156.5 mg of (*S*)-(+)-**5a**, $[\alpha]^{25}D$ +70° (*c* 0.82, 95% EtOH) [lit.[8] $[\alpha]^{25}D$ +70° (*c* 1.5, USP EtOH].

Registry No.—(*S*)-(+)-**1**, 53636-15-0; (*R*)-(−)-**2**, 57496-00-1; (*R*)-(−)-**2** HCl, 57496-01-2; (*S*)-(+)-**4a**, 7576-08-1; (*S*)-(+)-**5a**, 6134-96-9; diphenylacetonitrile, 86-29-3.

References and Notes

(1) M. Bockmühl and G. Ehrhart, *Justus Liebigs Ann. Chem.*, **561**, 52 (1949).
(2) E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948).

(3) A. H. Beckett, N. J. Harper, and J. W. Clitherow, *J. Pharm. Pharmacol.*, **15**, 349 (1963).
(4) A. H. Beckett and A. F. Casey, *J. Chem. Soc.*, 900 (1955).
(5) A. H. Beckett, G. Kirk, and R. Thomas, *Chem. Ind. (London)*, 1418 (1960).
(6) Inversion stereochemistry for the formation of aziridines and their ring opening by nucleophiles is well established. See O. C. Dermer and G. E. Ham, "Ethyleneimine and Other Aziridines," Academic Press, New York, N.Y., 1969, pp 26, 208, and references cited therein.
(7) Chlorination of 2-octanol with thionyl chloride and pyridine gave a more highly inverted chloride than when pyridine was absent: W. Gerrard and H. R. Hudson, *J. Chem. Soc.*, 1059 (1963).
(8) A. A. Larsen, B. F. Tullar, B. Elpern, and J. S. Buck, *J. Am. Chem. Soc.*, **70**, 4194 (1948).

Synthesis of 1,2,4-Triazoles from Tosylmethyl Isocyanide and Aryldiazonium Compounds[1]

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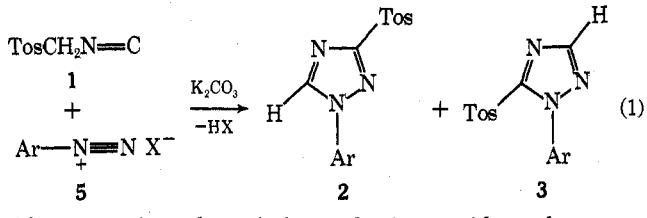
The coupling of diazonium salts and compounds XCH_2Y with an activated methylene group leads to formation of hydrazones. These reactions occur either without[3] or with loss (i.e. the Japp–Klingemann reaction)[4] of one of the activating functionalities X or Y. Ring-closed products are not usually formed in these processes.[3,4]

As a continuation of our work on synthetic applications of tosylmethyl isocyanide[5] (TosMIC, 1), we wish to report the synthesis of 1,2,4-triazoles from TosMIC and diazonium salts, according to eq 1. TosMIC accommodates, be-

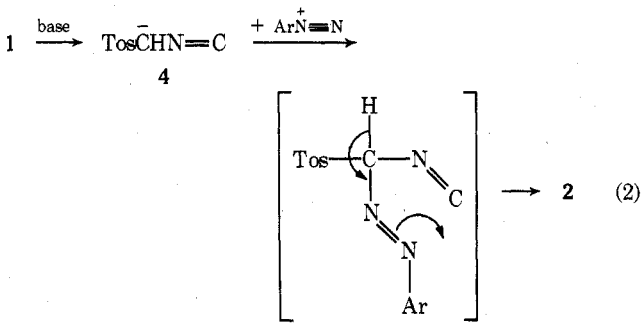


(1)

sides an activated methylene, the isocyanide carbon as a second reactive site. This offers the opportunity to form cyclic products. Thus, a number of azoles (oxazoles,[5a] imidazoles,[5b] thiazoles,[5c] and pyrroles[5d]) has been synthesized previously from TosMIC and C=O, C=N, C=S, and C=C containing substrates.[6]

It now appears that the N≡N triple bond of diazonium salts also is capable of undergoing cycloadditions with TosMIC[2,3] to give 1-aryl-3-tosyl-1,2,4-triazoles (**2**), together with minor amounts of the isomeric 1-aryl-5-tosyl-1,2,4-triazoles (**3**). The construction of the 1,2,4-triazole nucleus by this method, i.e., by formation of the N_1–C_5 and N_2–C_3 bonds, has a precedent in the Einhorn–Brunner reaction of diacylamines and hydrazines.[7]

The formation of the main product **2** is explained by eq 2, in close analogy with mechanisms proposed for previous

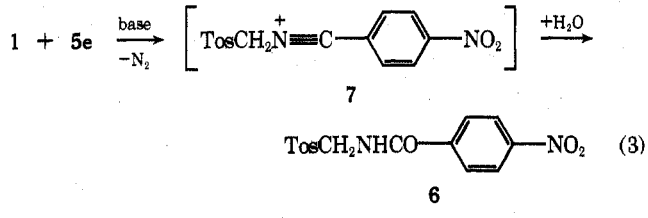


(2)

TosMIC reactions.[8] TosMIC anion **4** is assumed to attack the electrophilic β nitrogen of the diazonium ion, followed by ring closure and a proton shift to give **2**.

Several pathways are conceivable for the formation of the isomeric side-product **3**. These include, as an initial step, attack of TosMIC anion **4** at N_α rather than N_β of the diazonium ion, or, alternatively, attack at N_β by **4** through its isocyano carbon. Reaction through a diazotate anion, which also is present in the basic medium,[9] seems less likely since no **2c** (or **3c**) was formed from benzenediazonium tetrafluoroborate at pH > 13.[10] In fact, the formation of the triazoles **3** is the first illustration of a reversed addition of TosMIC to an unsaturated substrate.[8]

The reactions of TosMIC were carried out with a series of para-substituted benzenediazonium compounds, as well as with 3-pyridinediazonium chloride and α-naphthalenediazonium tetrafluoroborate (eq 1). As appears from Table I, that the highest yields of **2** were obtained from benzenediazonium salts with electron-donating substituents. A completely different reaction was observed with *p*-nitrobenzenediazonium tetrafluoroborate (**5e**). Instead of triazoles, the only product isolated was *N*-tosylmethyl-*p*-nitrobenzamide (**6**, 39%), apparently formed by nucleophilic displacement of nitrogen and hydration of the nitrilium ion[11] **7** (eq 3). For structural proof, **6** was prepared inde-



(3)

pendently (62% yield) by a Mannich condensation of *p*-toluenesulfinic acid, formaldehyde, and *p*-nitrobenzamide.

Structural Assignment of 2 and 3. The ^1H NMR, ir, and mass spectra of the isomers **2** and **3**, which were separable by preparative TLC, are consistent with the assigned structures (see Experimental Section). To differentiate between the substitution patterns in the isomeric triazoles,

Table I

		Compd 2		Compd 3	
Ar	X^-	% yield	Mp, °C	% yield	Mp, °C
a *p*-Dimethylaminophenyl	BF_4	94	177–178.5		
b *p*-Methoxyphenyl	Cl	80	144–145.5	12	141–142.5
c Phenyl	BF_4	40	120.5–122.5	18	112–114.5
d *p*-Acetylphenyl	BF_4	28	169–171.5	9	133.5–135.5
e *p*-Nitrophenyl[a]	BF_4				
f 3-Pyridyl	Cl	15	168.5–174[b]	3	127–128
g α-Naphthyl	BF_4	38	147.5–149.5		

[a] No triazole formed; see text and eq 3. [b] Dimorphous.