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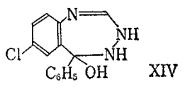
Heterocycles. VII.[1] Novel and Facile Syntheses of *s*-Triazolo-[4,3-*a*][1,4]benzodiazepine Derivatives

In previous papers,[1,2] we reported the syntheses of 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (*e.g.* XI and XII) which are potent central nervous system depressants.[3,4] This paper deals with novel and facile syntheses of these and related compounds.

Among several approaches to the new method for synthesizing XI and XII, we found that 3-amino-3,4-dihydroquinazolines (IVa, b)[5,6] are useful. These aminoquinazolines (IVa, b) were prepared from 2-amino-5-chlorobenzophenone (I) in two steps (Chart 1). Formylation of I with formic acid gave the formamido derivative (II), mp 92.5—93°.[7,8] Treatment of I with N,N-dimethyl-formamide or -acetamide and thionyl chloride or phosphorus oxychloride in chloroform gave amidines IIIa, mp 86—87°, and IIIb, mp 89—90°, while treatment with ethyl orthoacetate and acetic acid in boiling benzene gave an imido ester IIIc, mp 62—63°. When these II and III were allowed to react with hydrazine hydrate in ethanol, the aminoquinazolines IVa, mp 192—195°,[8] and IVb, mp 206—209°,[8] were obtained. The reaction with III was carried out in the presence of acetic acid as a catalyst. Each of the above-mentioned processes afforded yields of over 90%[except the reaction of IIIb→IVb (35%)].

1) Part VI: K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), in press.
2) K. Megro and Y. Kuwada, *Tetrahedron Letters*, **1970**, 4039; *idem*, *Chem. Pharm. Bull.* (Tokyo), in press.
3) R. Nakajima, C. Hattori, and Y. Nagawa, *Japan. J. Pharmacol.*, **21**, 489 (1971); R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui, and Y. Nagawa, *ibid.*, **21**, 497 (1971).
4) J.B. Hester, Jr., A.D. Rudzik, and B.V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971), also reported the synthesis and pharmacological activity of these compounds.
5) We had initially assigned a dihydro-1,3,4-benzotriazepine structure to these compounds (IVa, b) because of the identity of IVa which we prepared with compound XIV whose structure had been proposed by C. Podesva, G. Kohan, and K. Vagi, *Can. J. Chem.*, **47**, 489 (1969).



XIV

6) During the course of our investigation, a synthesis and structure determination of compounds IVa, b was reported by; *a*) M.E. Derieg, J.F. Blount, R.I. Fryer and S.S. Hillery, *Tetrahedron Letters*, **1970**, 3869; *b*) M.E. Derieg, R.I. Fryer, S.S. Hillery, W. Metlesics and G. Silverman, *J. Org. Chem.*, **36**, 782 (1971).
7) All melting points reported in this paper were measured with a Yanagimoto Micro Melting Point Apparatus (a hot stage type) and are uncorrected.
8) Reported melting points (see Ref. 6): II, mp 90—91°; IVa, 196—198° (decomp.); IVb, mp 218—219° (decomp.).

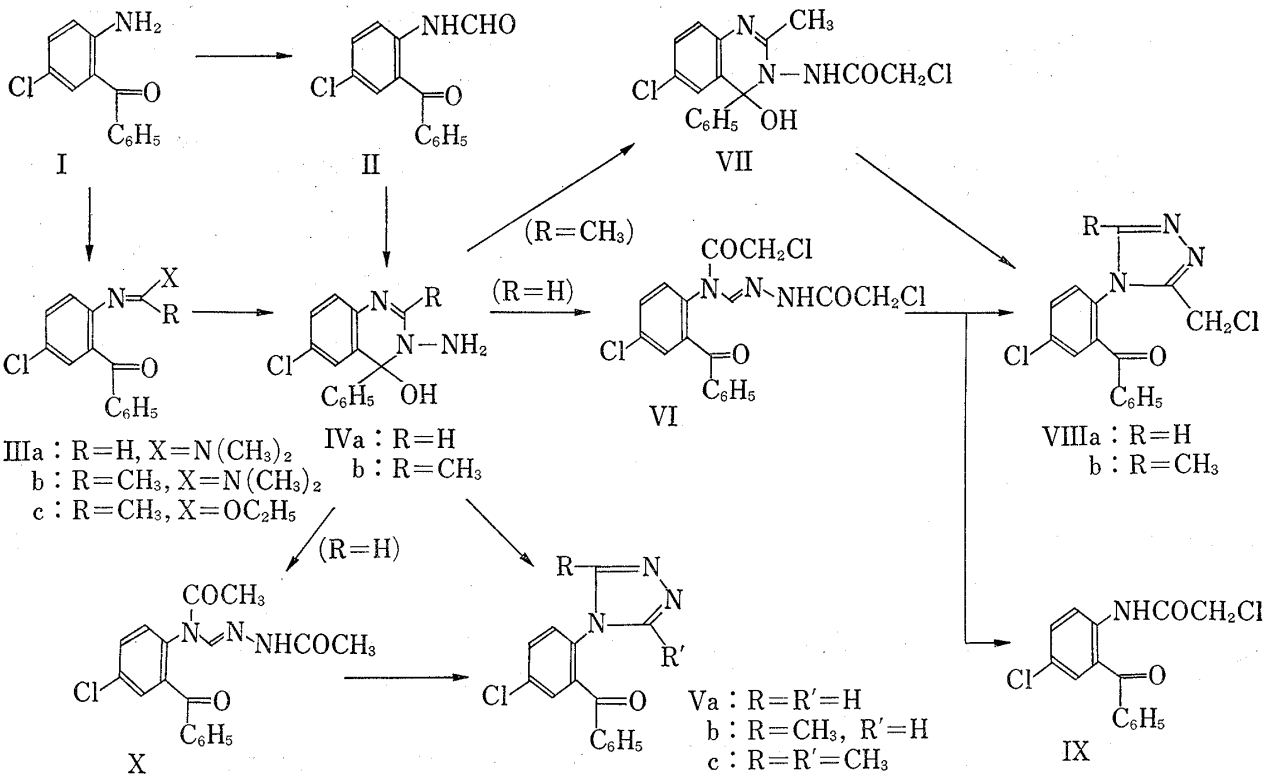


Chart 1

As might be expected, IVa and IVb may assume a tautomeric ring-opened form at the $N_{(3)}$-$C_{(4)}$ bond and they gave, on heating with formic acid, triazolylbenzophenones Va (32%), mp 167—169°,[9] and Vb (93%), mp 168—170°, respectively. Similarly Vc, mp 191—193° was obtained in 52% yield on treatment of IVb with acetic anhydride in acetic acid. These results suggested that an acyl derivative is an intermediate in the rearrangement of IV to a triazolylbenzophenone in an acidic medium, and prompted us to study the rearrangement of the chloroacetylation product of IV.

Chloroacetylation of IVa with chloroacetyl chloride in a mixture of chloroform and aqueous sodium carbonate furnished a bis (chloroacetyl) compound (VI), mp 159—160°, in 93% yield. The same compound (VI) was obtained in 89% yield by reaction of IVa with chloroacetic anhydride in pyridine. Ultraviolet (UV) spectrum of VI[10] was different from that of IVa and very similar to that of a diacetyl derivative (X) prepared by the method of Derieg, *et al.*[6] On heating with monochloroacetic acid in benzene, VI gave 5-chloro-2-(3-chloromethyl-4*H*-1,2,4-triazol-4-yl)benzophenone (VIIIa, 79%), mp 140—141° (hydrochloride: mp 176—178°), and in addition, 5-chloro-2-chloroacetamidobenzophenone (IX, 14%), mp 117—118°.[11] The separation of VIIIa and IX was easily effected by recrystallization. A similar reaction occurred with X to afford Vb (67%) and 2-acetamido-5-chlorobenzophenone (mp 116—117°, 10%).

After many attempts under a variety of conditions, chloroacetylation of IVb was finally achieved with chloroacetyl chloride in dry benzene in the presence of 2-methylimidazole.[12]

9) Syntheses of the same compound Va (mp 184—186°) have recently been reported by M.E. Derieg, R.I. Fryer and S.S. Hillery, *J. Heterocyclic Chem.*, **8**, 181 (1971).

10) UV spectra of IV, VI, VII, VIII and X are as follows: $\lambda_{max}^{iso\text{-}PrOH}$ nm (ε): IVa, 285.5 (11200); IVb, 286 (12100); VI, 254 (26900); VII (in MeOH), 279 (14000); VIIIa, 254 (13400); VIIIb, 255 (13600); X, 252 (28700).

11) Reported mp 117—118°. See L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

12) This reaction probably proceeds *via* a chloroacetyl imidazolide.

Thus the 3-chloroacetamidoquinazoline (VII), mp 127—129°, was obtained in 86% yield. Compound VII showed a similar UV spectrum to those of IVa and IVb,[10] and gave a chloromethyl-1,2,4-triazolylbenzophenone derivative (VIIIb), mp 143—144°, in 86% yield on heating in boiling formic acid.

Reaction of the key intermediates(VIIIa, b) with ammonia (or hexamethylenetetramine) and hydroxylamine resulted in the facile preparations of 4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepines (XI) (a: mp 230—231°; b: mp 230—231°) and their 5-oxides (XII) [a: mp 268—270° (decomp.); b: mp 273—274° (decomp.)], respectively. Treatment of VIII with aminoalcohols in boiling ethanol gave new tetracyclic oxazolo-[3,2-*d*]-*s*-triazolo[4,3-*a*][1,4]benzodiazepines (XIII) (a: mp 260—261°; b: mp 219—221°; c: mp 266—267°; d: mp 219—221°), which are active as central nervous system depressants.

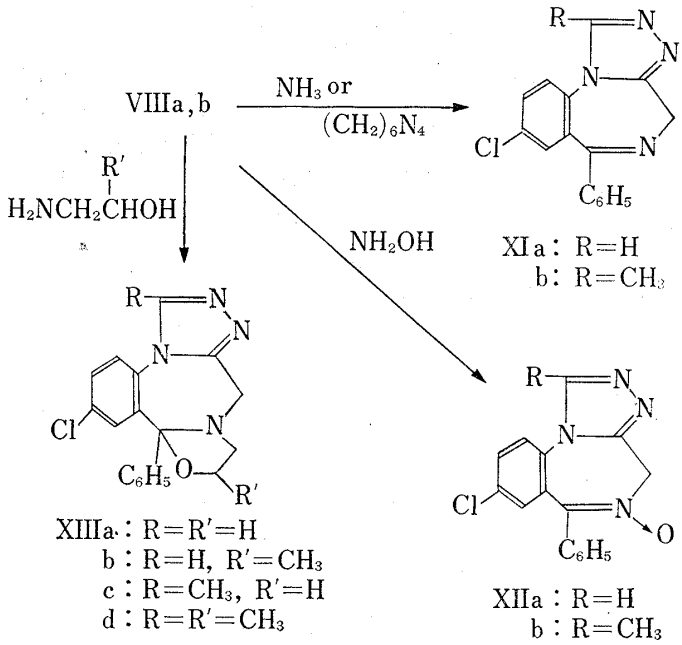


Chart 2

A series of analogs of XI, XII and XIII was synthesized similarly starting with 2-aminobenzophenones which contain a variety of substituents on the aromatic rings. The detailed syntheses and pharmacological activities of these as well as of the compounds reported in the present paper will be published in near future.

The structures of all compounds reported herein were supported by satisfactory elemental analyses and spectroscopic data.

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