(Darco). Removal of the methanol and crystallization from acetone–petroleum ether yielded 4.5 g (67%) of white prisms: mp 189–190°; $[\alpha]^{26}D$ −128°; infrared absorption ($CHCl_3$) at 3605 and 3500 (OH), 1723 (lactone C=O), and 1695 cm^{-1} (ketone C=O); nmr absorption ($CDCl_3$) at 340 Hz (singlet, 2 H, CH=CH).

Anal. Calcd for $C_{35}H_{60}O_{12}$: C, 62.48; H, 8.99; O, 28.54. Found: C, 62.41; H, 9.02; O, 28.47.

3′-De(dimethylamino)erythromycin B (8).—3′-De(dimethylamino)-3′,4′-dehydroerythromycin B (**6**, 930 mg) dissolved in 75 ml of absolute ethanol was stirred in a hydrogen atmosphere in the presence of 40 mg of Adams catalyst. After 30 min the theoretical amount of hydrogen was taken up and the solution was filtered. A tlc analysis (system A) of the filtrate showed a single new component. The volume was reduced to 7 ml and, when several drops of water were added, crystallization began. Filtration yielded 770 mg (83%) of 3′-de(dimethylamino)-erythromycin B (**8**): mp 194–198°; $[\alpha]^{26}D$ −113°; infrared absorption ($CHCl_3$) at 3604 and 3500 (OH), 1724 (lactone C=O), and 1696 cm^{-1} (ketone C=O).

Anal. Calcd for $C_{35}H_{62}O_{12}$: C, 62.29; H, 9.26; O, 28.45. Found: C, 62.35; H, 9.18; O, 28.46.

Sodium Borohydride Reduction and Glycoside Cleavage of 6 and 8.—The reduction and acid cleavage of **6** and **8** were carried out according to the procedure described for compounds **5** and **7**. From 1 g each of **6** and **8** was obtained 354 (59%) and 410 mg (68%), respectively, of 9-dihydroerythronolide B (**10**): mp 179–182° (from acetonitrile) (lit.[1e] mp 182°); $[\alpha]^{25}D$ +5.9° (lit.[1e] $[\alpha]^{25}D$ +6.0°); infrared absorption at 3614 and 3460 (OH), and 1699 cm^{-1} (lactone C=O).

For comparison, a sample of **10** was prepared from erythromycin B by the published procedure:[1e] mp 178–180° (lit.[1e] mp 182°); mixture melting point with **10** obtained from **6** and **8**, 178–180°. The infrared and nmr spectra, X-ray powder pattern, and tlc mobilities (systems A and B) of all three samples were identical.

The methyl glycosides were recovered from the filtrates of the crystallization of **10** by distillation (bp 55–70° at 0.2 mm) and compared by glpc to methyl glycosides obtained from **5** and **7**. The retention times of the methyl glycosides **11**, **12**, and **13** from **6** and **8** agreed within experimental error with the methyl glycosides from **5** and **7**, respectively. The nmr spectra of **12** and **13** isolated from **6** and **8** were identical with those shown in Figures 1 and 3.

The 3,5-dinitrobenzoate esters of the methyl glycosides **11** and **12** from **6** were prepared and separated by the previously described procedure. The ester of **13** (mp 148–150°, mmp 148–150°) and the ester of **11** (mp 157–162°, mmp 155–162°) were isolated and shown to be identical with the esters obtained from **5** by infrared and nmr spectra and tlc (system C).

Acknowledgment.—The authors wish to thank Drs. T. J. Perun and J. Tadanier for many helpful discussions and encouragement. Thanks are also due to Dr. M. Levenberg, Mrs. R. Stanaszek, and Mr. R. S. Egan for the nmr spectra, Mr. A. J. Kammer for the infrared spectra, Mrs. E. Baker, Miss J. Wolf, and Mr. D. Nelson for the tlc and glpc analyses, Mr. O. Kolsto and coworkers for elemental analyses, Mr. V. Poland for the X-ray patterns, and Mr. M. Freifelder and D. Dunnigan for carrying out the hydrogenations.

The Synthesis of 4,5-Dihydro-3H-1,3-benzodiazepines and 4,5-Dihydro-1H-2,4-benzodiazepines

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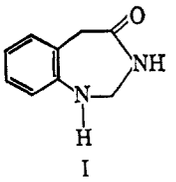
A general synthesis of dihydro-1,3- and -2,4-benzodiazepines has been devised. The method consists of the condensation of the appropriate diamine, *i.e.*, an *o*-aminophenethylamine or α,α'-diamino-*o*-xylene, respectively, with a wide variety of imidate hydrohalides. The effect of the structure of both the imidate hydrohalides and the diamines on the course of the reaction has been evaluated. The order of reactivity of the imidate hydrohalides toward condensation is haloalkyl ≫ alkyl > *p*-NO_2-aryl ≫ *p*-CH_3O-aryl. Steric crowding and decreased basicity of the diamine seriously retard the reaction. Solvent effects have also been explored. Alkylation experiments for the dihydro-1,3-benzodiazepine system indicate attack on the nitrogen, N-3, proven by independent synthesis. Additional chemistry of individual derivatives has been explored. Spectral data for both heterocyclic systems are reported.

Considerable attention has been directed in recent years to the synthesis of seven-membered ring compounds. Our particular interest in this area centered about the benzodiazepines. Syntheses of 1,2-, 1,4- and 1,5-benzodiazepines have been well worked out,[1-5] but 1,3- and 2,4-benzodiazepines have been only briefly explored. Plieninger[6] and Nogradi published a report in which a derivative form of a 1,3-benzodiazepine was synthesized. Later, deStevens[7] and Dughi reported on the synthesis of tetrahydro-1,3-benzodiazepines (I), but there has been no systematic study of the preparation of dihydro-1,3- and -2,4-benzodiazepines.



I

Dihydro-3H-1,3-benzodiazepines.—In accordance with procedures which proved successful for the synthesis of benzimidazoles[8] and quinazolines,[9] there exist for the synthesis of 1,3-benzodiazepines pathways *via* Scheme A, internal condensation of *o*-amino-N-acylphenethylamines or activated derivatives thereof,

(1) P. M. Maitlis in "Chemistry of Carbon Compounds," Vol. IVC, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, The Netherlands, 1960, pp 1581–1614.

(2) W. Ried and A. Draisbach, *Chem. Ber.*, **92**, 949 (1959); W. Ried and E. Torinus, *ibid.*, **92**, 2902 (1959).

(3) J. Thiele and G. Steimmig, *ibid.*, **40**, 955 (1907).

(4) The area of 1,4-benzodiazepines has been extensively explored by L. H. Sternbach and co-workers. For example, see L. H. Sternbach in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1965, pp 158–161.

(5) E. Fischer and H. Kuzel, *Ann.*, **221**, 294 (1883).

(6) H. Plieninger and I. Nogradi, *Chem. Ber.*, **88**, 1965 (1955).

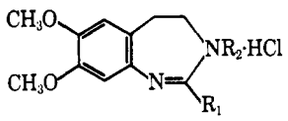
(7) G. deStevens and M. Dughi, *J. Amer. Chem. Soc.*, **83**, 3087 (1961).

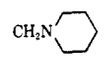
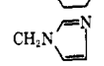
(8) K. Hofmann in "Chemistry of Heterocyclic Compounds: Imidazole and Derivatives," Vol. 6, Part I, Interscience Publishers, Inc., New York, N. Y., 1953, p 266.

(9) W. L. F. Armarego, *Advan. Heterocyclic Chem.*, **1**, 281 (1963).

TABLE I

DIHYDRO-3H-1,3-BENZODIAZEPINES[a]

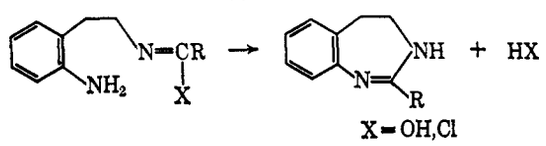


No.	R_1	R_2	Yield, %	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	CH_3	H	51	300	$C_{12}H_{16}N_2O_2 \cdot HCl$	56.16	56.03	6.67	7.02	10.94	10.69
2	CH_3	CH_3	56	267–269	$C_{13}H_{18}N_2O_2 \cdot HCl$	57.66	57.99	7.07	7.25	10.34	10.35
3	$CH_2C_6H_5$	H	48	194–196	$C_{18}H_{20}N_2O_2 \cdot HCl$	64.92	64.67	6.36	6.62	8.41	8.02
4	CH_2OCH_3	H	64	214–216	$C_{13}H_{18}N_2O_3 \cdot HCl$	54.44	54.79	6.67	6.83	9.76	9.68
5	C_6H_5	H	88	276–278	$C_{17}H_{18}N_2O_2 \cdot HCl$	64.04	64.20	6.00	6.32	8.79	8.42
6	C_6H_5	CH_3	52	267–268	$C_{18}H_{20}N_2O_2 \cdot HCl$	64.96	65.17	6.36	6.63	8.41	8.27
7	p-ClC_6H_4	H	34	273–276	$C_{17}H_{17}ClN_2O_2 \cdot HCl$	57.81	57.59	5.64	5.87	7.94	7.69
8	p-$CF_3C_6H_4$	H	36	281–282	$C_{18}H_{17}F_3N_2O_2 \cdot HCl$	55.86	55.53	4.81	5.12	7.24	7.08
9	p-$CH_3OC_6H_4$	H	38	243	$C_{18}H_{20}N_2O_3 \cdot HCl$	61.98	61.73	6.07	5.93	8.03	8.11
10	p-$O_2NC_6H_4$	H	41	200	$C_{17}H_{17}N_3O_4 \cdot HCl \cdot H_2O$	53.48	53.81	5.28	5.46	11.00	11.00
11	m-$O_2NC_6H_4$	H	36	262–264	$C_{17}H_{17}N_3O_4 \cdot HCl \cdot H_2O$	53.48	54.30	5.28	5.21	11.00	11.09
12	CH_2Cl	H	86	282	$C_{12}H_{15}ClN_2O_2 \cdot HCl$	49.50	49.72	5.54	5.88	9.63	9.60
13	$CH_2N(CH_3)_2$	H	63	248–250	$C_{14}H_{21}N_2O_2 \cdot 2HCl \cdot H_2O$	47.46	47.55	7.12	7.13	11.87	12.07
14		H	62	273–275	$C_{17}H_{25}N_3O_2 \cdot 2HCl$	54.20	54.19	7.18	7.48	11.20	11.24
15		H	65	269–271	$C_{15}H_{18}N_4O_2 \cdot 2HCl$	50.12	49.78	5.61	6.05	15.60	15.30
16	OH	H	79	244–247	$C_{11}H_{14}N_2O_3$	59.45	60.08	6.36	6.27	12.62	12.47
17	NH_2	H	34	200–203	$C_{11}H_{15}N_3O_2 \cdot HCl$	51.26	51.02	6.25	6.39	16.29	16.21

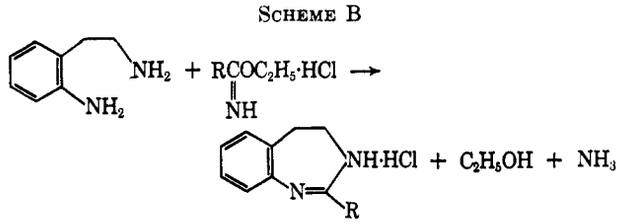
[a] All compounds were recrystallized from ethyl alcohol.

as well as Scheme B, bimolecular condensation of *o*-aminophenethylamines with carboxylic acids or their activated derivatives, especially imidate hydrohalides (Table I).

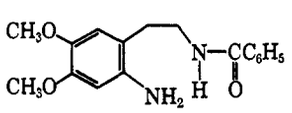
SCHEME A



SCHEME B



The former method initially appeared attractive owing to the ready availability of the necessary amides, mirroring the greater accessibility of the corresponding acid halides over the imidate hydrohalides. As a model compound, 2-amino-N-benzoyl-4,5-dimethoxyphenethylamine (II) was chosen because of its ease of synthesis through nitration of the commercially available homoveratrylamine, followed by benzoylation and reduction.



II

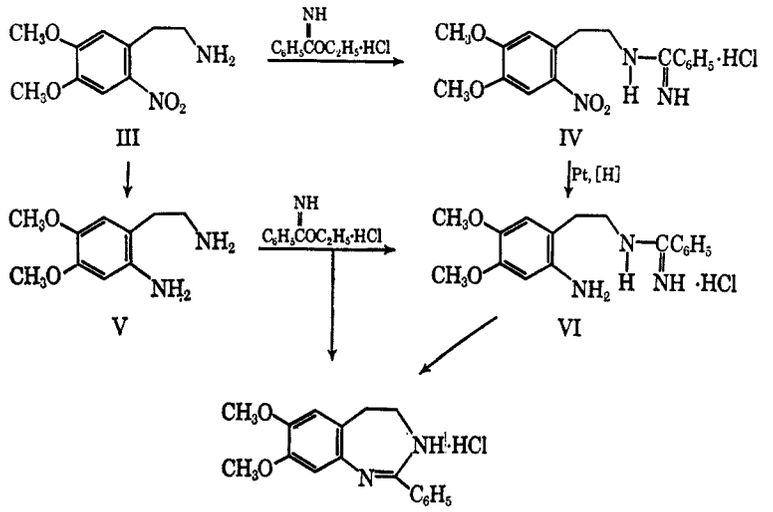
Cyclization was not achieved when II was heated above 200°. Below this temperature only starting material could be isolated. Acid catalysis with *p*-toluenesulfonic acid in refluxing xylene under azeotropic conditions again gave only starting material. In theory there remained the possibility of activating amide II by conversion to an imino chloride with a suitable reagent. Reflux of substance II in $POCl_3$ or $SOCl_2$, however, gave only intractable tars.

Attention was now turned to the reaction of an *o*-aminophenethylamine with an imidate hydrohalide (see Chart I). For this purpose, 2-amino-4,5-dimethoxyphenethylamine (V) was allowed to react with ethyl phenylimidate hydrochloride at reflux in ethanol. The original conditions chosen gave a very low yield of a product (5–10%) whose elemental analysis corresponded to the desired material, *i.e.*, 4,5-dihydro-7,8-dimethoxy-2-phenyl-3H-1,3-benzodiazepine hydrochloride (VII).

Reaction conditions which usually lead to an improvement in yield, such as increase in reaction time or temperature, were of no avail. Work-up of the mother liquors, however, gave an additional crop of crystals, which proved to be the condensation intermediate N-(2-amino-4,5-dimethoxyphenethyl)benzamidine hydrochloride (VI). It was determined that this intermediate would undergo ring closure merely by prior formation of the free basic amidine and then heating the latter compound under reflux in toluene for 24 hr. Attempts to form VI exclusively by controlling the conditions of the original reaction proved fruitless. Therefore, the condensation was performed with 2-nitro-4,5-dimethoxyphenethylamine (III) to give N-(4,5-dimethoxy-2-nitrophenethyl)benzamidine hydrochloride (IV). Catalytic reduction of IV with platinum gave exclusively VI which could then be transformed into the desired benzodiazepine VII in high yield.

The latter somewhat longer procedure was utilized for further derivatives until it was discovered that, in the 2-alkyl series, simple refluxing in ethanol of V with an alkyl imidate hydrochloride yielded the desired

CHART I

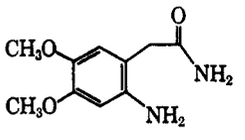


seven-membered ring compound. Reinvestigation of the 2-aryl series indicated that these conditions could be successfully employed depending upon the functionality in the phenyl imidate hydrochloride. It was shown that electron-withdrawing groups such as chloro and especially nitro groups enhanced the rate of reaction, and electron-donating groups such as methoxyl and alkyl groups retarded heterocycle formation, thus necessitating the use of the longer synthetic route.

This reaction, therefore, is typical of those having a positive ρ value,[10] a conclusion which is in agreement with that of DeWolfe and Augustine[11] in their work on the hydrolysis of ethyl benzimidates. Similarly, it was found that in the 2-alkyl series electron-withdrawing groups substituted on the alkyl group in the imidate ester, such as a chloro group, considerably enhanced the reaction rate, the reaction actually proceeding at room temperature.

Other factors which are noted to be of importance for the course of this condensation are steric and electronic in origin. Steric hindrance, in the nature of substitution on the basic amine function, seriously inhibited the condensation with the imidate. It was observed that the substitution of a methyl group on the primary amino group of V lowered the yield of the condensation with ethyl benzimidate hydrochloride from 80 to 10%.[12]

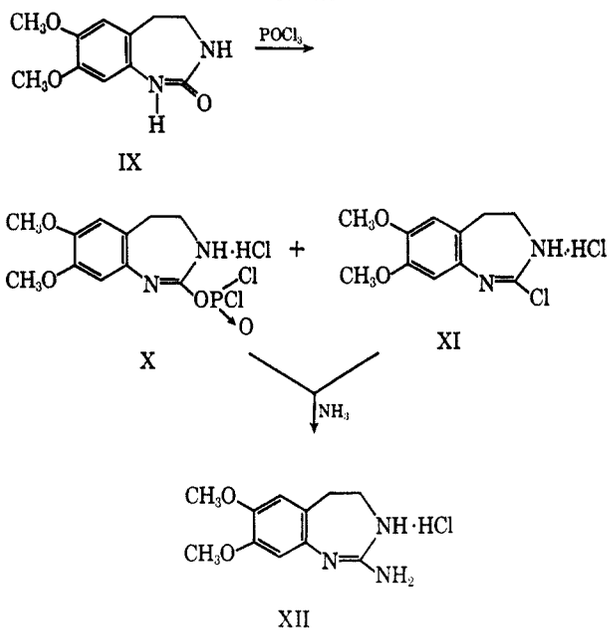
Another critical factor was found to be the basicity of the nitrogen atom which was to enter into condensation with the imidate. For example, it was observed that 2-amino-4,5-dimethoxyphenylacetamide (VIII) failed to react at all, even with the most reactive of the imidates utilized in this work, namely, ethyl chloroacetimidate hydrochloride.



VIII

It was also desirable in this series to prepare the cyclic urea, 2,3,4,5-tetrahydro-7,8-dimethoxy-1H-1,3-benzodiazepin-2-one (IX), and various derivatives thereof (see Chart II). It was found that N,N'-

CHART II



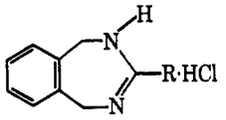
carbonyldiimidazole was a most useful reagent for this purpose, being far superior in this regard to urea or phosgene. Treatment of IX with refluxing $POCl_3$ resulted in a mixture of products, namely, X and XI. Both compounds individually or as crude mixtures readily underwent reaction with ammonia to afford the cyclic guanidine (XII).

A study of some reactions of 1,3-benzodiazepines was next undertaken. During experiments to replace the chloro group of 2-chloromethyl-7,8-dimethoxy-3H-1,3-benzodiazepine (XIII), it became apparent that the use of anything less than a very large excess of the nucleophilic reagent led to complex mixtures. It would seem reasonable that this phenomenon is due to the competition of the benzodiazepine ring itself toward replacement of the chloro group in a bimolecular reaction. The basis of this competition is probably a

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 220.
(11) R. A. DeWolfe and F. B. Augustine, *J. Org. Chem.*, **30**, 699 (1965).
(12) The yield could be raised to 25% by a change of solvent from ethanol to 1-butanol.

TABLE II

DIHYDRO-1H-2,4-BENZODIAZEPINES[a]

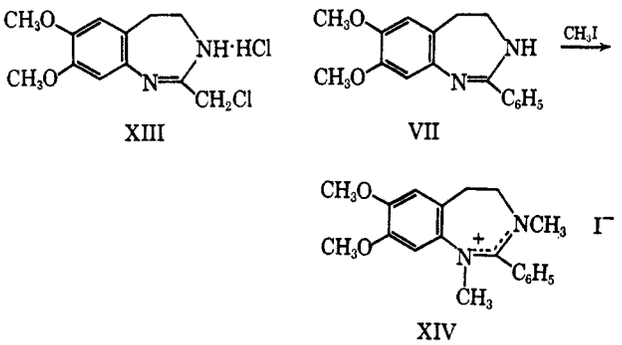


No.	R	Yield, %	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	CH_3	59	283–285	$C_{10}H_{12}N_2 \cdot HCl$	61.18	61.43	6.66	6.85	14.24	14.47
2	$CH_2C_6H_5$	67	256–259	$C_{16}H_{16}N_2 \cdot HCl$	70.44	70.38	6.28	6.11	10.27	10.46
3	CH_2OCH_3	28	175–178	$C_{11}H_{14}N_2O \cdot HCl$	58.29	58.00	6.64	6.82	12.36	12.33
4	CH_2Cl	53	263–264	$C_{10}H_{11}ClN_2 \cdot HCl$	61.70	61.69	5.70	5.81	14.39	14.15
5	$CH_2N(CH_3)_2$	78	239–241	$C_{12}H_{17}N_3 \cdot 2HCl$	52.18	52.36	6.93	6.94	15.27	15.04
6	OH	84	>300	$C_9H_{10}N_2O$	66.64	66.84	6.21	6.34	17.27	17.06
7	$OPOCl_2$	72	215	$C_9H_9Cl_2N_2O_2P \cdot HCl$	34.44	34.20	3.28	3.26	8.71	8.80
8	NH_2	76	279–281	$C_9H_{11}N_3 \cdot HCl$	54.66	54.42	6.12	6.24	21.25	21.05
9	$N(CH_3)_2$	69	253–255	$C_{11}H_{15}N_3 \cdot HCl$	58.55	58.22	7.15	7.44	18.62	18.58
10	*p*-ClC_6H_4	46	266–267	$C_{15}H_{13}ClN_2 \cdot HCl$	61.44	61.15	4.82	4.64	9.55	9.34
11	*p*-$O_2NC_6H_4$	36	278–280	$C_{15}H_{13}N_3O_2 \cdot HCl$	59.30	59.06	4.64	4.90	14.83	14.76
12	*m*-$O_2NC_6H_4$	55	260	$C_{15}H_{13}N_3O_2 \cdot HCl$	59.30	59.58	4.64	4.67	14.83	14.49
13	*p*-$CF_3C_6H_4$	58	>300	$C_{16}H_{13}F_3N_2 \cdot HCl$	58.82	58.94	4.32	4.29	8.57	8.49

[a] All compounds were recrystallized from ethyl alcohol.

consequence of the well-recognized superior basicity of the amidine system over secondary amines.

Theoretically, there are two possible sites of attack for an alkylating agent in a 1,3-benzodiazepine. Experiments were undertaken to determine this position. It was found that attempts to alkylate VII with methyl iodide at room temperature afforded only starting material, whereas, at elevated temperatures, there were obtained mixtures which consisted of starting material and fully methylated material (XIV).

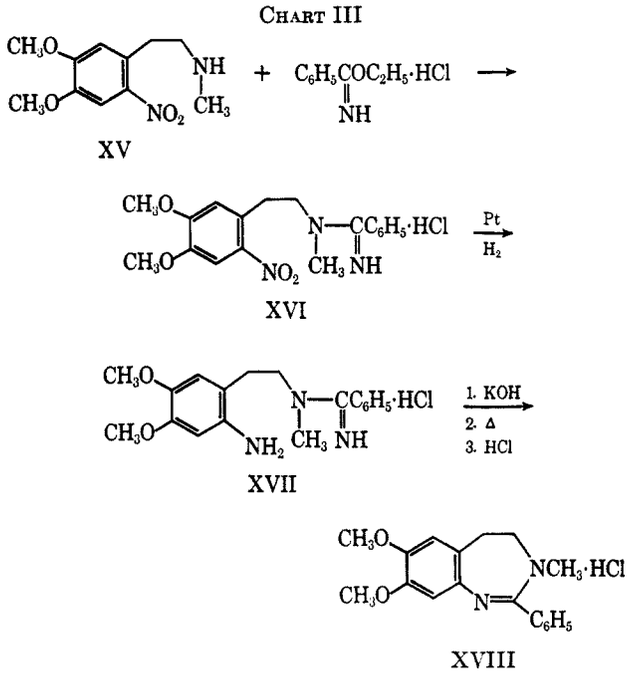


XIII VII XIV

However, the monomethylated product could be formed in 80% yield by treating VII with *n*-butyllithium, followed by condensation with methyl *p*-toluenesulfonate. Spectral analysis of the product to determine the position of alkylation proved to be inconclusive. Therefore, it was decided to prepare one of the two possible derivatives, *i.e.*, the 3-N-methyl derivative, by an independent and unequivocal route (see Chart III).

Condensation of 3,4-dimethoxy-N-methyl-1-nitrophenethylamine (XV) with ethyl benzimidate hydrochloride gave a low yield of amidine hydrochloride (XVI) which, after catalytic reduction to the corresponding amine (XVII), followed by ring closure in the usual manner, gave a compound (XVIII) which proved to be identical in all respects with the monoalkylated material described above. Thus, the position of initial attack in alkylation by this procedure (utilizing *n*-butyllithium and methyl *p*-toluenesulfonate) is the nitrogen in the 3 position. This proved to be the case

CHART III



XV XVI XVII XVIII

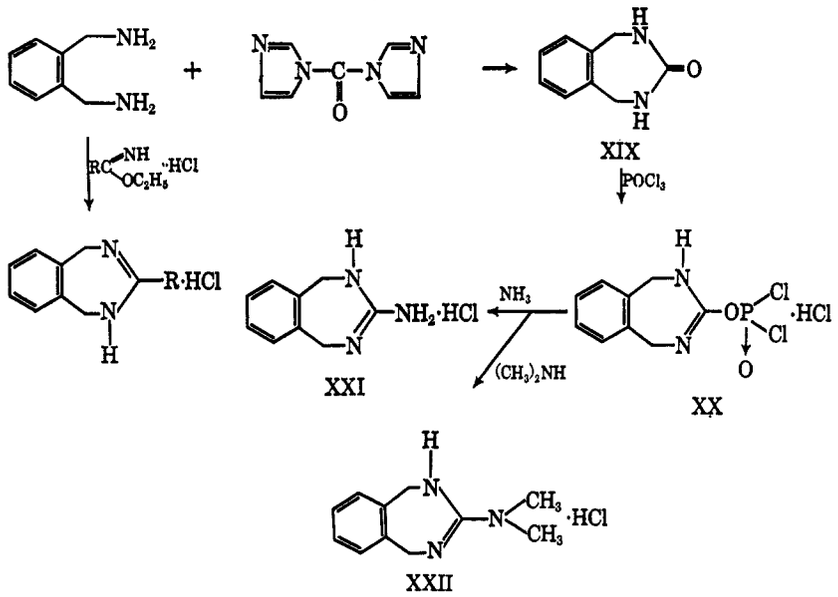
not only in the 2-aryl series but in the 2-alkyl series as well.

Dihydro-1H-2,4-benzodiazepines.—It was also noteworthy that the area of dihydro-1H-2,4-benzodiazepines was relatively unexplored, although representative examples of the 2,4-diazepine system were found only in derivative form, namely, dibenzodiazepines[13] and dinaphthodiazepines[14] (Table II).

In order to synthesize the parent ring system it was necessary to begin with α,α'-diamino-*o*-xylene, the preparation of which has already been described.[15] However, as heated tube conditions are necessary, this approach was deemed unsuitable for the large-scale preparations needed for research in this area. Experiments were inaugurated to determine the feasibility of hydrolysis of α,α'-diphthalimido-*o*-xylene using the

(13) W. Ried and A. Sinhray, *Chem. Ber.*, **98**, 3523 (1965).
(14) W. Ried and J. Braeutigam, *ibid.*, **99**, 3304 (1966).
(15) H. Strasseman, *ibid.*, **21**, 576 (1888).

CHART IV



method of Ing and Manske[16] whereby the phthalimide is allowed to react with hydrazine and the resulting intermediate is then acid hydrolyzed. Initial experiments failed due to the high insolubility of the diphthalimide in ethanolic hydrazine. By changing the solvent to the higher boiling 1-butanol, the method was found to give excellent yields (85%) of α,α'-diamino-*o*-xylene under normal laboratory conditions.

Condensation of the α,α'-diamino-*o*-xylene with various imidates yielded the desired dihydro-2,4-benzodiazepines in all cases with ease. This series was found to parallel the dihydro-1,3-benzodiazepine series completely in these preparations. The order of reactivity of the imidates, *i.e.*, chloromethyl > alkyl > aryl, was found to hold. However, in each case the rate of reaction was always greater than in the 1,3 series, a fact which probably can best be explained by the greater nucleophilicity of the corresponding alkylamine *vs.* the arylamine toward ring closure in the final step of the reaction.

Similarly, it was shown that reaction of α,α'-diamino-*o*-xylene with N,N'-carbonyldiimidazole yielded the desired 2,3,4,5-tetrahydro-1H-2,4-benzodiazepin-3-one (XIX). Reaction of this compound with $POCl_3$, however, gave only a single substance, the phosphoryl derivative (XX) of the starting material (XIX). The former compound reacted in fair yield with ammonia and dimethylamine to afford the desired guanidines (see Chart IV).

Again as in the 1,3-benzodiazepine series, reaction of 3-chloromethyl-4,5-dihydro-1H-2,4-benzodiazepine with secondary amines was successful only in the event that a large excess of amine was used. In contrast, however, to the 1,3 series, treatment of 3-*p*-chlorophenyl-4,5-dihydro-1H-2,4-benzodiazepine (XXIII) with 1 equiv of *n*-butyllithium and then 1 equiv of methyl *p*-toluenesulfonate did not afford a monomethyl derivative. Only complex mixtures were obtained and no pure material could be isolated. Several variations of this procedure did not give rise to the desired product.

(16) H. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2349 (1926).

Spectral Analysis.—The infrared spectra exhibited peaks at 1650–1680 and 1610–1625 cm^{-1} for the 1,3-benzodiazepines. The same double absorption in this region, somewhat displaced, *i.e.*, 1630–1650 and 1605–1620 cm^{-1}, was also found to be characteristic of the 2,4-benzodiazepines.

The nmr spectra of both series were normal giving typical chemical shifts for functional groups present, such as methoxyls, aromatics, alkyls, etc. It was found, however, that to obtain the correct number of replaceable protons, it was necessary to run the spectra in trifluoroacetic acid solution. Solvents such as DMF and DMSO tended to give low values, sometimes as low as one replaceable proton when actually two are present in the compound.

The uv spectra of the 1,3-benzodiazepines were characterized by three absorptions: λ_{max} 220–230 mμ (ϵ 21,000–24,000), 276–284 (8000–9000), and 292–305 (8500–10,600). The 2,4-benzodiazepines exhibited only aromatic absorption at λ_{max} 240 mμ (ϵ 18,000).

Experimental Section

Melting points are uncorrected and were determined with a Hoover melting point apparatus. The infrared spectra were determined as Nujol mulls with a Perkin-Elmer infrared spectrophotometer, Models 21 and 251. Ultraviolet spectra were determined on a Cary 14 recording spectrophotometer. Nuclear magnetic resonance spectra were determined in trifluoroacetic acid solution with a Varian A-60 nmr spectrometer.

Preparation of Imidic Acid Ester Hydrochlorides.—All imidates utilized throughout this research effort were prepared from the corresponding nitriles according to the method of Pinner.[17] The following were synthesized: ethyl acetimidate hydrochloride, mp 300° (lit.[17] mp 298°); ethyl chloroacetimidate hydrochloride, mp 90° (lit.[18] mp 92°); ethyl phenylacetimidate hydrochloride, mp 127° (lit.[11] mp 129°); ethyl methoxyacetimidate hydrochloride, mp 109–112° (lit.[19] mp 110°); ethyl benzimidate hydrochloride, mp 129–130° (lit.[11] mp 128–129°); ethyl *p*-chlorobenzimidate hydrochloride, mp 175–177° (lit.[11] mp 178°); ethyl *p*-nitrobenzimidate hydrochloride, mp 194–195° (lit.[11] mp 192–194°); ethyl *m*-nitrobenzimidate hydrochloride, mp 135° (lit.[11] mp 135–136°); ethyl *p*-anisimidate hydrochloride, mp 130–131°

(17) A. Pinner, *Chem. Ber.*, **16**, 1654 (1883).

(18) S. M. McElvain and U. J. Nelson, *J. Amer. Chem. Soc.*, **64**, 1825 (1942).

(19) H. G. Sule, *J. Chem. Soc.*, **113**, 9 (1918).

(lit.[11] mp 130°); **ethyl *p*-trifluoromethylbenzimidate hydrochloride**, mp 125° (new compound).

Anal. Calcd for $C_{10}H_{10}F_3NO \cdot HCl$: C, 47.33; H, 4.38; N, 5.52. Found: C, 47.07; H, 4.56; N, 5.60.

4,5-Dimethoxy-2-nitrophenethylamine (III). Nitration of Phenethylamines.—The nitration of homoveratrylamine was performed according to the method of Mason,[20] *i.e.*, nitration in aqueous nitric acid. It was found in this laboratory, however, that this method fails to be convenient when the resultant nitrated product does not precipitate out of the reaction mixture. This was found to be the case with 3,4-dimethoxy-N-methylphenethylamine. A method was therefore developed which proved to be convenient and to afford high yields. This consisted of the utilization of trifluoroacetic acid as a medium. The high acidity of the medium enhanced the yield and its volatility facilitated the ease of isolation of the product. Use of 1 equiv of nitric acid (present as the amine salt) proved to minimize side effects.

To a solution of 50.0 g (0.26 mol) of 3,4-dimethoxy-N-methylphenethylamine[21] in 100 ml of ethanol was added nitric acid dropwise, with ice cooling, just until neutralization occurred. Upon further cooling the nitrate salt was obtained in a quantitative yield as yellow crystals, mp 78–80°.

Anal. Calcd for $C_{11}H_{17}NO_2 \cdot HNO_3$: C, 51.16; H, 7.03; N, 10.86. Found: C, 51.35; H, 7.29; N, 10.61.

The salt was then dissolved in 200 cc of trifluoroacetic acid and the yellow solution was warmed in a water bath to approximately 40° at which time the reaction became exothermic. The solution darkened and the temperature rose to the boiling point of trifluoroacetic acid. After the reaction subsided, the excess trifluoroacetic acid was removed *in vacuo;* the residue was dissolved in water, made strongly basic with saturated KOH, and extracted well with $CHCl_3$; the extracts were dried over K_2CO_3 and evaporated to give 40.0 g of an oil. The oil was dissolved in 300 ml of ethanol and made acidic with ethanolic hydrogen chloride to give 40.8 g (71%) of the hydrochloride as yellow crystals, mp 205–208°.

Anal. Calcd for $C_{11}H_{16}N_2O_4 \cdot HCl$: C, 47.73; H, 6.19; N, 10.11. Found: C, 47.38; H, 6.30; N, 10.40.

General Preparation of Dihydro-1,3-benzodiazepines. Route 1.—To a solution of 80.0 g (0.35 mol) of 4,5-dimethoxy-2-nitrophenethylamine (III) in 750 ml of methyl alcohol was added 66.0 g (0.35 mol) of ethyl benzimidate hydrochloride. The solution was refluxed for 3 hr and then concentrated to a small volume. Trituration gave a yellow solid which was recrystallized from ethyl alcohol to give 85.0 g (66%) of IV as yellow crystals, mp 241–243°.

Anal. Calcd for $C_{17}H_{19}N_3O_4 \cdot HCl$: C, 55.81; H, 5.51; N, 11.48. Found: C, 55.60; H, 5.49; N, 11.43.

The solid was slurried in 1 l. of ethyl alcohol. The slurry was hydrogenated over 1 g of PtO_2 at an initial pressure of 45 psi. The colorless solution was filtered under N_2 and evaporated to an oil which was dissolved in water. The aqueous solution was made strongly basic and extracted with $CHCl_3$. The extracts were dried over K_2CO_3 and evaporated to an oil which was redissolved in toluene (1 l.). The toluene solution was refluxed overnight with the evolution of ammonia. The solution was then concentrated *in vacuo* to an oil which was triturated with ethyl acetate to give a brown solid. This material was recrystallized from ethyl acetate twice with the aid of decolorizing charcoal to give 65.3 g (88%) of light tan crystals, mp 107–109°. A sample was dissolved in ethanol and made acidic with ethanolic hydrogen chloride to give 4,5-dihydro-7,8-dimethoxy-2-phenyl-3H-1,3-benzodiazepine hydrochloride (VII) as white crystals, mp 276–278°.

Route 2.—A solution of 8.0 g (0.04 mol) of III in 200 ml of ethanol was reduced with 1 g of PtO_2 at an initial pressure of 45 psi. The colorless solution was filtered under N_2 and to this was added directly 9.5 g (0.04 mol) of ethyl *p*-trifluoromethylbenzimidate hydrochloride. The solution was then refluxed for 20 hr and concentrated to give a white solid which was recrystallized from ethyl alcohol–methyl alcohol to give 5.3 g (36%) of **4,5-dihydro-7,8-dimethoxy-3-*p*-trifluoromethylphenyl-3H-1,3-benzodiazepine hydrochloride** as white crystals, mp 281–282°.

2,3,4,5-Tetrahydro-7,8-dimethoxy-1H-1,3-benzodiazepin-2-one (IX).—A solution of 20.0 g (0.09 mol) of III in 350 ml of THF was hydrogenated with 2.0 g of PtO_2 at an initial pressure of 45 psi. The solution was filtered under N_2 and to this was added directly 14.5 g (0.09 mol) of N,N′-carbonyldiimidazole with ice cooling. The solution was allowed to stand overnight at room temperature and then was refluxed for 2 hr. The solid which formed was filtered and recrystallized from a large volume of water to give 14.0 g (79%) of white material, mp 244–247°.

2-Amino-4,5-dihydro-7,8-dimethoxy-3H-1,3-benzodiazepine Hydrochloride (XII).—A slurry of 25.0 g (0.12 mol) of IX was made in 25 ml of $POCl_3$ which was then kept at 95–100° for 1 hr. The solution was cooled and diluted with ethyl acetate to give 20.2 g of a tan solid which exhibited a wide melting point range. Elemental analysis indicated that the mixture consisted of a 3:1 ratio of X and XI.

Addition of the mixture directly to 200 cc of liquid ammonia gave upon evaporation of the liquid ammonia at room temperature a white solid. Dissolution in hot water and basification with saturated KOH gave a semisolid which was separated from the supernatant by decantation. This was dissolved in a large volume of $CHCl_3$ and dried over K_2CO_3. Evaporation of the solvent *in vacuo* gave an oil which was dissolved in ethanol and made acidic with ethanolic hydrogen chloride to give 10.6 g (34%) of white crystals, mp 233°.

4,5-Dihydro-7,8-dimethoxy-2-dimethylaminomethyl-3H-1,3-benzodiazepine Dihydrochloride.—A solution of 18.0 g (0.06 mol) of XIII was made in a minimum amount of boiling water. The solution was cooled in ice to room temperature and was made strongly basic with saturated KOH. The precipitate was filtered and air dried. Recrystallization from benzene gave 12.3 g (80%) of tan crystals, mp 126°.

Anal. Calcd for $C_{12}H_{15}ClN_2O_2$: C, 56.47; H, 5.09; N, 10.98. Found: C, 56.29; H, 5.67; N, 10.93.

The chloromethyl free base obtained in this manner was refluxed for 2 hr in 50 ml of methanol saturated with dimethylamine. The solution was evaporated and the solid redissolved in ethanol to which was added ethanolic hydrogen chloride until acidic. The precipitate was filtered and washed with ethanol to give 10.1 g (63%) of white crystals, mp 248–250°.

4,5-Dihydro-7,8-dimethoxy-3-methyl-2-phenyl-3H-1,3-benzodiazepine Hydrochloride (XVIII). Route 1.—A solution of 10.0 g (0.04 mol) of the free base of VII was dissolved in 250 ml of toluene and refluxed for 3 hr under a Dean–Stark apparatus. The solution was cooled and 24 ml of 1.6 *N* *n*-BuLi was added under N_2 all at once with stirring. Stirring was continued for 45 min and then 5 ml (0.04 mol) of methyl *p*-toluenesulfonate was added all at once. The solution was then stirred overnight and stripped *in vacuo* to a small volume. Chloroform and water were then added and the layers separated. The organic layer was then dried over K_2CO_3 and evaporated to an oil which was dissolved in ethanol and made acidic with ethanolic hydrogen chloride to give 6.1 g (52%) of a tan solid, mp 267–268°.

Route 2.—A solution of 5.0 g (0.02 mol) of 4,5-dimethoxy-N-methyl-2-nitrophenethylamine (XV) in 25 ml of ethyl alcohol was refluxed for 17 hr with 3.9 g (0.02 mol) of ethyl benzimidate hydrochloride. The solution was concentrated to an oil and triturated with ethyl acetate to give 5.5 g of a solid melting at 160–180°. The solid was triturated again with chloroform to give after filtration 2.2 g (29%) of XVI as a yellow solid, mp 218–219°.

Anal. Calcd for $C_{18}H_{21}N_3O_4 \cdot HCl$: C, 56.92; H, 5.84; N, 11.06. Found: C, 56.69; H, 5.76; N, 10.93.

A slurry of 2.5 g (0.01 mole) of XVI was made in 50 ml of ethyl alcohol and then the slurry was hydrogenated with 0.5 g of PtO_2. The colorless solution was filtered under N_2 and evaporated to an oil *in vacuo*. The oil was dissolved in a minimum amount of water and the aqueous solution was made strongly basic with saturated KOH. The solution was extracted well with $CHCl_3$ and the extracts were dried over K_2CO_3. The solvent was stripped *in vacuo* to give an oil which was heated in 50 ml of toluene for 24 hr. The toluene was stripped *in vacuo* to give an oil whose hydrochloride was formed in the usual manner (1.5 g, 68%), mp 268–270°. This compound proved to be identical in all respects with XVIII. Mixture melting point with the substance from route 1 above gave no depression.

4,5-Dihydro-7,8-dimethoxy-1,3-dimethyl-2-phenyl-3H-1,3-benzodiazepinium Iodide (XIV).—4,5-Dihydro-7,8-dimethoxy-2-phenyl-1H-1,3-benzodiazepine (2.0 g, 0.007 mol) was heated at reflux in 50 ml of benzene with 1.0 g (0.007 mol) of methyl iodide for 1 hr. The solid was filtered to give 1.8 g (59%) of XIV, mp 187°.

(20) J. A. Mason, *J. Chem. Soc.*, 200 (1953).

(21) J. S. Buch, *J. Amer. Chem. Soc.*, **52**, 4119 (1930).

Anal. Calcd for $C_{19}H_{23}N_2O_2 \cdot I$: C, 51.92; H, 5.51; N, 6.38. Found: C, 51.68; H, 5.61; N, 6.32.

α,α′-Diphthalimido-o-xylene.—A mixture of 500 g (1.9 mol) of α,α′-dibromo-o-xylene, 1 kg (5.4 mol) of potassium phthalimide, and 3.78 l. of DMF was stirred and refluxed for 16 hr. The mixture was then cooled to approximately 100° and diluted with an equal volume of water. The precipitate was then filtered, washed well with water, ethyl alcohol, and ether, consecutively, and air-dried to give 606 g (81%) of white, fluffy crystals, mp 275° (lit.[15] mp 277°).

α,α′-Diamino-o-xylene Dihydrochloride.—A slurry of 200 g (0.51 mol) of α,α′-diphthalimido-o-xylene was made in 7 l. of 1-butanol. To this was added 48.5 ml (0.98 mol) of 99% hydrazine hydrate and the mixture was stirred and refluxed for 16 hr. With continued stirring and refluxing, 100 ml (1.12 mol) of concentrated HCl was added and reflux was continued for 24 hr. At this time approximately one-half the solvent was evaporated *in vacuo*. The white solid formed was filtered and then triturated with 500 cc of water. The water was stripped *in vacuo* and the residue was triturated with methanol. After filtration the white solid was recrystallized from 4:1 ethanol–water to give 89.5 g (84%) of white crystals, mp >300° (lit.[15] mp >300°).

Preparation of Dihydro-2,4-benzodiazepines.—A solution of 2.0 g (0.015 mol) of α,α′-diamino-o-xylene (prepared from the dihydrochloride by extraction with $CHCl_3$ of a strongly alkaline aqueous solution) in 40 ml of ethyl alcohol was refluxed overnight with 1.8 g (0.015 mol) of ethyl acetimidate hydrochloride. The solution was cooled overnight to give 1.7 g (59%) of **4,5-dihydro-3-methyl-1H-2,4-benzodiazepine hydrochloride** as white crystals, mp 283°.

To a solution of 2.0 g (0.015 mol) of α,α′-diamino-o-xylene in 25 ml of methyl alcohol was added 2.3 g (0.015 mol) of ethyl chloroacetimidate hydrochloride. The solution was allowed to stand overnight. The solution was then added dropwise with stirring to a large excess of ether to give 1.8 g (53%) of 3-chloromethyl-4,5-dihydro-1H-2,4-benzodiazepine hydrochloride, mp 255°.

2,3,4,5-Tetrahydro-1H-2,4-benzodiazepin-3-one (XIX).—To a solution of 6.0 g (0.044 mol) of α,α′-diamino-o-xylene in 150 ml of THF was added 7.5 g (0.046 mol) of N,N′-carbonyldiimidazole in 100 cc of THF dropwise with ice cooling. The solution was then allowed to stand overnight at room temperature. The white solid was filtered to give 6.0 g (84%), mp 300°.

4,5-Dihydro-3-dimethylaminomethyl-1H-2,4-benzodiazepine Dihydrochloride.—The pH of a concentrated aqueous solution of 3-chloromethyl-2,5-dihydro-1H-2,4-benzodiazepine hydrochloride (10.0 g, 0.043 mol) was adjusted to approximately 9. The precipitate was collected on a filter, washed well with water, air-dried, and recrystallized from ethyl acetate to give 4.5 g (54%) of the free base, mp 235–240°.

Anal. Calcd for $C_{10}H_{11}N_2Cl$: C, 61.70; H, 5.70; N, 14.39. Found: C, 61.98; H, 5.76; N, 14.58.

To a saturated solution of dimethylamine in methyl alcohol (15 ml) was added 4.5 g of the chloromethyl free base. The solution was refluxed for 0.5 hr. This was then made acidic with ethanolic hydrogen chloride and the solid formed was recrystallized from ethyl alcohol to give 5.0 g (78%) of white crystals, mp 239–241°.

3-Amino-4,5-dihydro-1H-2,4-benzodiazepine Hydrochloride (XXI).—A slurry of 7.5 g (0.046 mol) of XIX in 30 ml of $POCl_3$ was heated on a water bath for 3 hr. The excess reagent was evaporated *in vacuo* and the solid triturated with ethyl acetate and filtered to give 11.0 g (72%) of XX, mp 215°. This material was added in portions to 200 ml of liquid ammonia. The slurry was stirred while the ammonia was allowed to evaporate naturally at room temperature over a 3-hr period. The remaining solid was slurried in water, made strongly basic with saturated KOH, and extracted with chloroform. The extracts were dried over K_2CO_3 and evaporated to an oil. This was dissolved in ethanol and made acidic with ethanolic hydrogen chloride. The solution was evaporated to give white crystals which were recrystallized from ethanol–methanol to give 5.0 g (76%) of XXI, mp 279–281°.

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Studies on Chrysanthemic Acid. I. Some Reactions of the Isobutenyl Group in Chrysanthemic Acid

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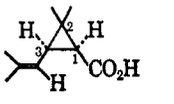
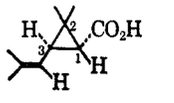
Diphenyloxetane derivatives were prepared by photocycloaddition of *cis*- and *trans*-chrysanthemic acid (**1a** and **1b**) to benzophenone. Oxidation of the *cis* isomer (**1a**) with lead tetraacetate afforded an olefinic γ-lactone (**11**), which was hydrolyzed to the corresponding olefinic hydroxy acid (**12**). The *trans* isomer (**1b**) gave an epoxide (**7**) by oxidation with monoperphthalic acid, while the *cis* isomer did not react at all with this reagent. Amino functions were introduced into the isobutenyl group by applying the Ritter reaction to **1a** and **1b** and by ring opening of **7** with dimethylamine.

A number of ester derivatives of chrysanthemic acid[1] have been reported mainly because of interest in their insecticidal activity.[2] It is known that the isobutenyl group of chrysanthemic acid is rather unreactive toward cycloaddition reactions; **1a** and **1b** give only a trace of pyrazoline esters even with excess amounts of diazomethane[3] and, furthermore, Diels–Alder additions with maleic anhydride or cyclopentadiene and the dichlorocarbene addition thereto are all unsuccessful.[4]

In this paper we describe the results of some reactions carried out successfully on the isobutenyl group of **1a** and **1b**, including the photocycloaddition with benzophenone, oxidations with lead tetraacetate and monoperphthalic acid, and the Ritter reaction.



1a



1b

Results and Discussion

Photocycloaddition.—Irradiation of **1a** with benzophenone in benzene or methanol afforded in low

(1) Chrysanthemum monocarboxylic acid, 2,2-dimethyl-3-isobutenylcyclopropane-1-carboxylic acid (the *cis* isomer (**1a**) and the *trans* isomer (**1b**)).

(2) For example, see (a) Y-L. Chen and W. F. Barthel, *J. Am. Chem. Soc.*, **75**, 4287 (1953); (b) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958); (c) W. F. Barthel, U. S. Patent, 2,857,309 (1958); *Chem. Abstr.*, **53**, 8528*d* (1959); (d) T. Mitsui and T. Nagase, *J. Sci. Res. Inst.* (Tokyo), **50**, 76 (1956); *Chem. Abstr.*, **51**, 7639*d* (1957); (e) T. Mitsui, M. Kitahara, and T. Nagase, *J. Sci. Res. Inst.* (*Tokyo*), **50**, 80 (1956); *Chem. Abstr.*, **51**, 7639*e* (1957).

(3) I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 283 (1945).

(4) T. Sasaki, S. Eguchi, and M. Ohno, unpublished observation.