renes.[7] It is not yet certain whether the stereospecific dehydroiodinations of the 2-benzenesulfonyl-3-iodobutanes fall in this category or in the concerted 2b category.[47] It seems certain, however, that the dehydrofluorination of fluorobenzene with sodamide falls in this category.[28b]

If *cis* eliminations are admitted, the dehydrohalogenation data of the *trans* compounds of Table IV are consistent with 14b. In contrast, Cristol takes $k_6 = 0$ and uses isomerization step 5.[7] The following line of reasoning argues for *cis* elimination in the case of *trans*-dibromoethene. The ratio

$$k_{elim}^{C}/k_{elim}^{T} = k_1k_8k_3/k_7k_2k_{5,6} \qquad (15)$$

is 5×10^5; $k_{5,6}$ corresponds either to elimination by path 5 (and 3) or by path 6. Taking $k_2 \simeq k_8$ and $k_1/k_7 \simeq 50$, $k_3 \simeq 10^{13}$ sec.$^{-1}$. This corresponds to ~5.5 kcal./mole in free energy of activation. Now if $k_6 > k_5$, $V > 5.5$ kcal./mole and if $k_6 < k_5$, $V = 5.5$ kcal./mole.[48] The barrier to *cis–trans* conversion is not expected to differ drastically from the barrier to *trans–cis* conversion. Since the minimum in V has been set at 28 kcal./mole, we conclude $k_6 > k_5$ and *cis*-dehydrobromination of the *trans*-dibromoethene occurs.

cis–trans pairs of compounds in this category exhibit large rate ratios as in expression 15. Although this may be attributed mainly to k_3/k_6, a more detailed analysis of the activation parameters must be deferred until more data on the individual steps are available. It would appear, however, that the theory of minimum orbital bending provides a quantum mechanical rationalization for the prediction that $k_3/k_6 > 1$.[49]

The preceding discussion of base-catalyzed eliminations emphasizes that apparently similar systems may eliminate by different paths. Alternative one-, two- or three-step mechanisms must be considered for any specific case. Perhaps the most interesting experimental problem to be solved here revolves around the fate of the vinyl carbanion: will it lose halide, isomerize or abstract a proton from the solvent?

(47) P. S. Skell and J. H. McNamara, THIS JOURNAL, **79**, 85 (1957).

(48) This approach to (15) was suggested by a referee who correctly argued by somewhat different assumptions that the isomerization barrier was given by $V > 11$ kcal./mole.

(49) G. H. Stewart and H. Eyring, *J. Chem. Educ.*, **35**, 550 (1958).

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE EASTERN LABORATORY OF E. I. DU PONT DE NEMOURS AND CO.]

Liquid Phase Nitration of Bicyclo[2.2.1]heptane and Decahydronaphthalene

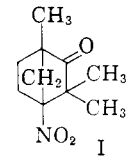
BY GEORGE W. SMITH

RECEIVED MAY 17, 1958

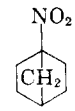
The liquid phase nitration of bicyclo[2.2.1]heptane (norbornane) by nitrogen dioxide in carbon tetrachloride was investigated under various conditions to determine the positions attacked and the amounts of the mononitro derivatives formed. The major nitro compound formed was 2-nitrobicyclo[2.2.1]heptane which was isolated in conversions as high as 30%. Vapor phase chromatography and infrared analysis suggest that very small amounts (<1.0% conversion) of two other mononitro derivatives (alkali-insoluble) may have been formed in the reaction. The nitration of decahydronaphthalene was carried out under similar conditions to give a 9.0% yield of 9-nitrodecahydronaphthalene.

Substitution reactions involving bridgehead carbons have been of theoretical interest for some time. A review of the available literature to June, 1954, concerning this subject indicated the difficulty encountered in such displacement reactions.[1]

In 1915, Nametkin and co-workers reported that liquid phase nitration of camphane, isocamphane and camphenilane with dilute nitric acid at 140° yielded only secondary nitro derivatives and some ketones and dibasic acids.[2] No bridgehead nitro compounds were isolated in these experiments. However, *d*-fenchone was reported to yield both a secondary and a tertiary nitro compound when allowed to react with dilute nitric acid at 130°.[3] The tertiary nitro derivative was believed by Nametkin to be the bridgehead compound I. More recently the vapor phase nitration of bicyclo[2.2.1]heptane at 400° by concentrated nitric acid was reported to give nitronorbornane of which approximately 50% was the bridgehead derivative II.[4] In view of the



I



II

results reported concerning the nitration of bicyclo[2.2.1]heptane derivatives, the liquid phase nitration of bicyclo[2.2.1]heptane was investigated with nitrogen dioxide as the nitrating agent and with conditions somewhat more vigorous than those used in previous liquid phase work to determine where substitution would occur.

Carbon tetrachloride was employed as a solvent for both bicyclo[2.2.1]heptane (a solid) and nitrogen dioxide in all runs except one in which gaseous nitrogen dioxide (preheated to 175°) was fed into the autoclave. After a relatively short reaction period (16–23 min.), 2-nitrobicyclo[2.2.1]heptane was obtained in conversions as high as 30%. The identity of this major product as the 2-nitro derivative was confirmed by infrared and elemental analyses. These results are in agreement with those obtained in the chlorination of bicyclo[2.2.1]heptane

(1) D. E. Applequist and J. D. Roberts, *Chem. Revs.*, **54**, 1065 (1954).

(2) S. Nametkin, *et al.*, *J. Russ. Phys. Chem. Soc.*, **47**, 409 (1915).

(3) S. Nametkin, *J. prakt. Chem.*, [2] **108**, 29 (1924).

(4) R. T. Blickenstaff and H. B. Hass, THIS JOURNAL, **68**, 1431 (1946).

in which case norbornyl chloride (2-chloronorbornane) was the main product.[5]

The best conversions to 2-nitrobicyclo[2.2.1]-heptane occurred when the mole ratio of norbornane to nitrogen dioxide employed was two (see Table I). Attempts to increase the amount of nitration in positions other than the 2-position by increasing the reaction temperature above 200° resulted in greater tar formation with no apparent change in the point of attack.

The amounts of *endo* and *exo* isomers of 2-nitrobicyclo[2.2.1]heptane present in the original product were not determined. However, the product which was purified for elemental analysis and whose infrared spectrum appears in Fig. 1 should be largely the *exo* isomer, because this material was isolated by regeneration of the nitro form from the potassium salt of the aci form. Roberts, Lee and

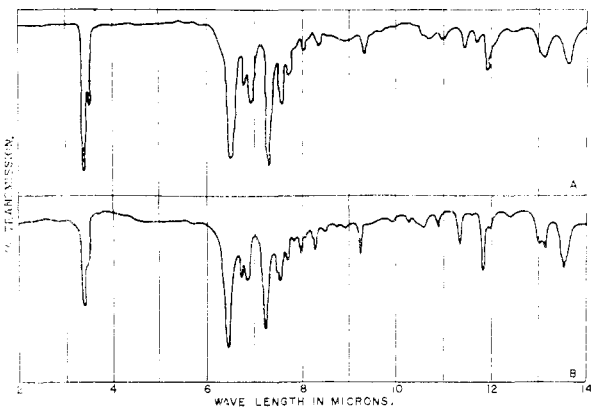


Fig. 1.—A, Infrared spectrum of an authentic sample of 2-nitrobicyclo[2.2.1]heptane in CCl_4 (2–12 μ) and CS_2 (12–14μ); B, infrared spectrum of a melt sample of 2-nitrobicyclo[2.2.1]heptane isolated from nitration reaction.

Saunders showed that the regeneration of the salt of the aci form of 2-nitrobicyclo[2.2.1]heptane in an isomerization experiment with *endo*-2-nitrobicyclo[2.2.1]heptane yielded a mixture of 70–80% *exo* and 30–20% *endo*.[6]

All nitration reactions yielded small amounts of alkali-insoluble material (see Table I). The alkali-insoluble product isolated from one nitration run was examined by infrared analysis and vapor phase chromatography. The infrared spectrum showed that the major functional group bands consisted of a strong doublet band (5.65 and 5.68 μ) in the carbonyl region and two nitro group bands of approximately equal intensity at 6.43 and 6.51 μ. The position of the nitro group band in the spectrum of 2-nitrobicyclo[2.2.1]heptane falls at 6.47 μ (see Figs. 1 and 2). Vapor phase chromatography showed that three major components and two very minor components (larger retention time) were present in the alkali-insoluble mixtures.

Of the three major components the one eluted first appeared in the region of norcamphor and the other two (approximately equal concentrations) were eluted almost simultaneously in the same pre-

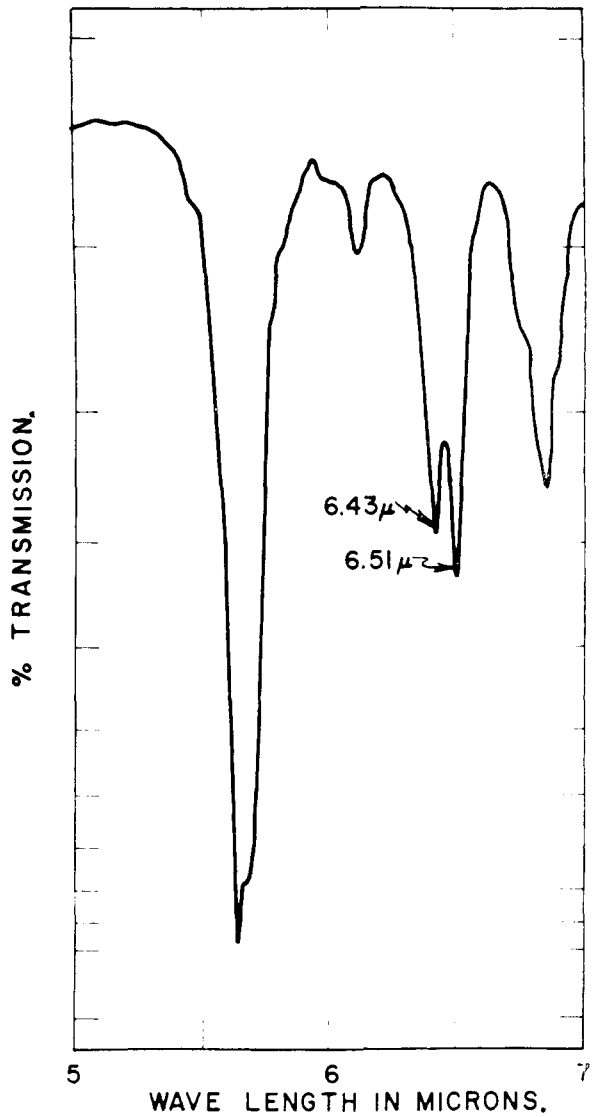


Fig. 2.—Infrared spectrum of capillary film of alkali-insoluble product.

cise region that 2-nitrobicyclo[2.2.1]heptane was found to be eluted. These results, *i.e.*, the relative positions of the components in the vapor chromatogram and the concentrations of the components as indicated by both infrared analysis and vapor chromatography, suggest that the major components of the alkali-insoluble material are ketobicyclo[2.2.1]heptane,[7] and possibly 1-nitrobicyclo[2.2.1]heptane and 7-nitrobicyclo[2.2.1]heptane. The latter compound might not be readily soluble in base because of the strain present at carbon-7. Nitrocyclopropane, for example, was reported to be affected only very slightly when treated by a base. This lack of reactivity toward bases and the weak acidity was ascribed to the internal strain involved in the conversion of small ring nitrocycloalkanes into its nitronate anion or its nitronic acid.[8] No definite assignment of nitro absorption bands can be given to a particular isomer

(5) J. D. Roberts, L. Urbanek and R. Armstrong, THIS JOURNAL, **71**, 3049 (1949).

(6) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

(7) The spectrum of an authentic sample of 2-ketobicyclo[2.2.1]-heptane showed that the carbonyl absorption occurs at 5.7μ.

(8) H. B. Hass and H. Shechter, THIS JOURNAL, **75**, 1382 (1953).

at this time. However, on the basis of the results reported concerning the position of the nitro group asymmetrical stretching band of about 150 compounds, one might tentatively assign the 6.51 μ to 1-nitrobicyclo[2.2.1]heptane and the 6.43 μ band to 7-nitrobicyclo[2.2.1]heptane.[9]

The nitration of commercial decahydronaphthalene was carried out under conditions similar to those used for the nitration of bicyclo[2.2.1]heptane. Although no bridgehead carbons are present in this hydrocarbon, it was of interest to determine the extent of nitration in the tertiary position. At a reaction temperature of 120°, a 9.0% yield (based on the amount of hydrocarbon consumed) of the tertiary derivative, 9-nitrodecahydronaphthalene, was obtained. No accounting of the secondary nitro derivatives was made.

The results related above once again illustrate the difficulty encountered in substitution at bridgehead carbons of small bridged ring compounds. When similar experimental conditions were used, the amount of tertiary nitration in decahydronaphthalene (no bridgehead carbons) approached the statistical value; whereas, in the case of bicyclo-[2.2.1]heptane, only trace amounts of tertiary substitution were indicated. Also of interest is the observed resistance of carbon-7 toward substitution.

Experimental

Nitration of Bicyclo[2.2.1]heptane (Norbornane).—Bicyclo[2.2.1]heptane, b.p. 110–111° (760 mm.), and carbon tetrachloride were charged to an autoclave in 1:1 molar amounts and heated to 150–200° at a constant pressure of 300 p.s.i.g. At the desired reaction temperature, a cooled solution (0–5°) of nitrogen dioxide in carbon tetrachloride was fed into the reaction zone from a charge reservoir by means of a Milton Roy feed pump. After a reaction period of 16–48 minutes, the reaction mixture was cooled to room temperature. Two slightly different procedures were employed in the isolation of the products. In procedure A the reaction mixture was extracted directly by an equal volume of 5% sodium hydroxide solution for approximately 4 hours. The carbon tetrachloride solution then was washed by two portions of water and dried over anhydrous magnesium sulfate. The dried solution subsequently was concentrated to obtain the alkali-insoluble products. The secondary nitro compounds were regenerated by neutralization of the sodium hydroxide extract. In procedure B the reaction mixture was washed successively by water and several portions of 5% sodium bicarbonate solution until neutral. The washed carbon tetrachloride solution then was dried over anhydrous magnesium sulfate. After removing most of the carbon tetrachloride by distillation at atmospheric pressure, the reaction products, which consisted mainly of 2-nitronorbornane, were distilled at reduced pressure (1–2 mm.). The distilled products were extracted by a 5–10% sodium hydroxide solution, and the alkali-insoluble portion was taken up in ethyl ether and dried over anhydrous magnesium sulfate. See Table I for a summary of these experiments.

TABLE I

LIQUID PHASE NITRATION OF BICYCLO[2.2.1]HEPTANE BY NITROGEN DIOXIDE[a]

Moles of norbornane	Vol. of CCl_4, ml.[b]	Moles of NO_2	Vol. of CCl_4 in feed, ml.[c]	Temp., °C.	Reaction time, min.	% conversion to 2-nitronorbornane	Wt. of alkali-insol. material, g.
2.0	300	2.0[d]	..	175–200	30	9.0	2.7
1.0	150	1.0	150	180–195	38	5.0	..
1.5	150	0.75	100	180–190	16	30[e]	0.5
1.5	150	.78	100	180–190	33	..[f]	1.0
1.5	150	.75	100	145–155	25	..[f]	2.0
1.0	100	1.0	150	150–160	22	14[g]	2.3
1.5	150	0.75	100	150	23	28[h]	3.0
1.5	150	.75	100	180	48	..[f]	1.7
1.5[i]	150	.75	100	180–190	66	8.5	1.5

[a] All runs were carried out at 300 p.s.i.g. unless otherwise noted. [b] Solvent for norbornane. [c] Solvent for nitrogen dioxide. [d] Nitrogen dioxide was preheated to 175° before feeding into reaction zone. [e] Refractive index of the product was $n^{25}D$ 1.4810. [f] Secondary nitro compound was not isolated. All runs yielded a small quantity of alkali-insoluble material which consisted of a mixture of nitro and carbonyl compounds. [g] The product in this run was isolated by regenerating the free nitro compound from a sodium hydroxide solution, according to the procedure of Kornblum and Graham. [h] Refractive index of the product was $n^{23}D$ 1.4810. [i] This run was carried out at 600 p.s.i.g.

Isolation of 2-Nitrobicyclo[2.2.1]heptane. Procedure B.—The product from the last run listed in Table I was worked-up according to procedure B as described above. After distillation of the carbon tetrachloride, the monosubstituted bicyclo[2.2.1]heptane derivatives were distilled through a small packed column at 1–2 mm. pressure and collected over the range 55–69°. The colorless product weighed 13.3 g. and possessed a refractive index $n^{25}D$ 1.4828 which agreed with the value reported[10] for 2-nitrobicyclo-[2.2.1]-heptane ($n^{20}D$ 1.4843).

A portion of this material (11.0 g.) was mixed with 25 ml. of methyl alcohol, 25 ml. of water and 5.0 g. of potassium hydroxide with cooling and agitation at room temperature for 16.0 hr. The basic solution then was diluted with 50 ml. of water and extracted by diethyl ether. The ether extract was washed by water until neutral and finally dried over anhydrous magnesium sulfate. Concentration of the dried ether solution yielded 1.5 g. of a pale yellow liquid.

The basic solution from above was placed in a three-necked flask equipped with a thermometer and an addition funnel. After cooling to 0°, 43 ml. of an aqueous solution of acetic acid and urea[11] was added dropwise while the temperature was maintained at 0–2° according to the procedure of Kornblum and Graham.[12] The resulting cold reaction mixture was extracted by diethyl ether and the ether extract was washed by 5% sodium bicarbonate and water until neutral and dried over anhydrous magnesium sulfate. Subsequent removal of the ether afforded 7.5 g. of a cream-colored solid. Sublimation of this sample at approximately 20 mm. and 70° yielded a white waxy solid, m.p. 74–76° (sealed capillary).[13]

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.53; H, 7.73; N, 9.99.

The infrared spectrum of this compound compared favorably with the spectrum of an authentic sample of 2-nitrobicyclo[2.2.1]heptane (see Fig. 1). The authentic sample of the 2-nitro derivative consisted mainly of the *endo* isomer. As mentioned earlier, the above sample, m.p. 74–76°, should be largely the *exo* isomer, although some of the *endo* isomer may also be present. It appears to make little difference in the infrared spectrum if *exo-endo* mixtures are used.

Analysis of Nitration Products.—The infrared analyses were made on a Perkin–Elmer model 21 spectrophotometer using sodium chloride optics with the exception of the spectrum of the authentic sample of 2-nitrobicyclo[2.2.1]heptane which was made on a Baird instrument. The vapor phase chromatography was performed on an F & M Scientific Corporation high temperature vapor fractometer (model 17A). The products were passed over a 5-ft. silicone on Celite column at 199°.

The vapor chromatogram of the alkali-insoluble product from the last run listed in Table I showed that five components were present. The retention times for these compo-

(9) J. F. Brown, Jr., THIS JOURNAL, **77**, 6341 (1955). Nitrobicyclo-[2.2.1]heptene might be offered as a possible candidate for one of the unknown nitro compounds. However, nitroölefins generally give a nitro group absorption at a significantly higher wave length than those reported above.

(10) W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, **17**, 1641 (1952).

(11) Concentration was 20.5 g. of urea per 102 g. of 20% acetic acid.

(12) N. Kornblum and G. Graham, THIS JOURNAL, **73**, 4041 (1951).

(13) The melting point of *endo*-2-nitrobicyclo[2.2.1]heptane-3-C^{14} was reported as not too well defined with most of the material melting at 64–67°.[6]

nents under the conditions employed in our experiments were 34, 59, 62, 77 and 95 seconds. The component with the shortest retention time is ketobicyclo[2.2.1]heptane, and the other two major products with retention times of 59 and 62 seconds are believed to be the 1-nitro- and 7-nitrobicyclo-[2.2.1]heptanes. The vapor chromatogram showed that these latter two components were present in almost equal concentrations. The retention time for the alkali-soluble 2-nitrobicyclo[2.2.1]heptane under conditions identical to those employed above was 58 seconds. The minor components of the alkali-insoluble product were eluted at retention times of 77 and 95 seconds. In addition to the carbonyl and nitro bands found in the infrared spectrum of this sample a weak doublet at 2.83 and 2.87μ indicated the presence of some hydroxy compound.

Nitration of Decahydronaphthalene.—A 207-g. (1.5 moles) sample of decahydronaphthalene (n^{25}D 1.4694) was charged to a 1-liter stainless steel autoclave, pressured to 300 p.s.i.g. and heated to 120°. At this point 34.5 g. (0.75 mole) of nitrogen dioxide dissolved in 100 ml. of carbon tetrachloride (0–5°) was fed into the reaction zone by means of a Milton Roy feed pump. After a total reaction period of 1 hour (50 minutes feed and 10 minutes cook), the autoclave was cooled to room temperature. The reaction mixture was washed first with 150 ml. of water and then extracted with a 5% sodium hydroxide solution for 18 hours. The alkali-insoluble portion was washed with water and dried over anhydrous magnesium sulfate. Distillation of the dried solution at reduced pressure yielded 122.4 g. (59% recovery) of decahydronaphthalene, b.p. 70° (14 mm.), 32.1 g. of higher-boiling material (n^{25}D 1.4929–1.5010), and a pot residue weighing 16.7 g. The 32.1-g. portion of the distillate was extracted by 130 ml. of 10–15% sodium methoxide for 2.5 hours. The mixture then was diluted with 200 ml. of water, extracted by four 75-ml. portions of diethyl ether, and dried over anhydrous magnesium sulfate. Distillation of the alkali-insoluble material yielded 10 g. of 9-nitrodecahydronaphthalene, b.p. 60–65° (0.2 mm.). This amount of product represents a 9.0% yield based on the amount of decahydronaphthalene consumed. The infrared spectrum of the product coincided with that of 9-nitrodecahydronaphthalene which was reported previously.[14] Also, the refractive index of the product (n^{25}D 1.4925) was in excellent agreement with that reported in the literature.[14-16]

Acknowledgments.—The author wishes to thank Mr. L. J. Lohr for the interpretation of the infrared spectra and the vapor phase chromatographic work, and Prof. J. D. Roberts for supplying infrared spectra of authentic samples of 2-nitronorbornane and norcamphor.

(14) D. K. Brayn, Dissertation, Ohio State University, 1954.
(15) S. Nametkin and D. Madaev-Ssichev, *Ber.*, **59B**, 370 (1926).
(16) W. Hückel and M. Blohm, *Ann.*, **502**, 114 (1933).

GIBBSTOWN, N. J.

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORP.]

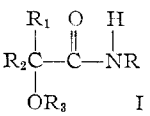
α-Hydroxy Amides and Related Compounds

BY SEYMOUR L. SHAPIRO, IRA M. ROSE AND LOUIS FREEDMAN

RECEIVED MAY 21, 1959

A series of α-hydroxyamides and the corresponding alkyl carbonate esters of type I have been synthesized and examined for anticonvulsant activity. The best activity has been noted with the N-aralkyl glycolamides. The spectra of I, where R is phenyl and substituted phenyl, have been determined and compared with the analogous acetanilides.

While a wide variety of recent studies of carboxylic acid amides has shown pharmacological activity,[1] there has been relatively little systematic exploration[2] of the amides of α-hydroxy acids. Studies[3] of such amides, and derivatives of these compounds of the type I are herein described.



I

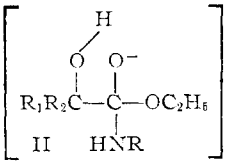
R = alkyl, aralkyl, aryl
R_1, R_2 = H, CH_3, C_6H_5

R_3 = hydrogen (H)
$-COOCH_3$ (M)
$-COOC_2H_5$ (E)
$-COOC_3H_7$-*n* (P)
$-COO(CH_2)_2Cl$ (CE)
$-COO(CH_2)_3Cl$ (CP)

Interest in the structures I (R_3 = H) was indicated from the noted therapeutic usefulness of the related acetanilides[4] and the potential for conversion of I to substituted oxazolidinediones.[5] In turn, the variant of I employing the carbonate esters (R_3, other than H), was introduced to afford more lipophilic structures of varying hydrolytic stability.[6] In addition, the carbonate esters were required as intermediates for conversion to carbamates.

The compounds prepared have been described in Table I. Some variants of I are detailed in the Experimental section.

Most of the amides (I, R_3 = H) were prepared by ammonolysis of the ethyl esters of the α-hydroxy acids (method A).



II

This is a relatively complex reaction, responsive to steric factors and the basicity of the amine, and is promoted by the α-hydroxy group in the acylating

(1) (a) S. R. Safir, H. Dalalian, W. Fanshawe, K. Cyr, R. Lopresti, R. Williams, S. Upham, L. Goldman and S. Kushner, THIS JOURNAL, **77**, 4840 (1955); (b) H. Rosen, A. Blumenthal, P. N. Townsend, R. Tislow and J. Seifter, *J. Pharmacol. Exp. Therap.*, **117**, 488 (1956); (c) F. Ascoli Marchetti and M. L. Stein, *Gazz. chim. ital.*, **84**, 816 (1954); (d) C. Malen and J. R. Boissier, *Bull. soc. chim. France*, 923 (1956); (e) H. Martin and H. Zutter, U. S. Patent 2,773,899 (Dec. 11, 1956); (f) H. Martin and E. Habicht, U. S. Patent 2,848,364 (Aug. 19, 1958); (g) R. I. Hewitt and L. H. Taylor, U. S. Patent 2,877,154 (Mar. 10, 1959).

(2) (a) H. McIlwain, "Chemotherapy and the Central Nervous System," Little, Brown and Co., Boston, Mass., 1957, p. 67; (b) F. A. Grunwald, U. S. Patent 2,764,613 (Sept. 25, 1956).

(3) For related work see S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **81**, 3083 (1959).

(4) A. Burger, "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1951, pp. 196–199.

(5) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin and L. Freedman, THIS JOURNAL, **81**, Dec. 20, (1959).

(6) The order of decreasing hydrolytic stability would be estimated as R_3 = CE, M, E, P; see (a) K. H. Vogel and J. C. Warner, *ibid.*, **76**, 6072 (1953); (b) A. A. Colon, K. H. Vogel, R. B. Carlin and J. C. Warner, *ibid.*, **75**, 6075 (1953).