TABLE I.—AMIDES PREPARED

| Amide | M.P., °C. | Yield Based on Amine, % | Kjeldahl Nitrogen Calcd., % | Kjeldahl Nitrogen Found, % |
|---|---|---|---|---|
| N-β-Phenethyl-β-phenyl-α-benzyloximinopropionamide | 54–56 | 55.3 | 7.53 | 7.52[a] 7.54 |
| N-β-(3,4-Dimethoxyphenethyl)-β-phenyl-α-benzyloximinopropionamide | 46–48 | 40.3 | 6.48 | 6.47 6.35 |
| N-β-(3,4-Methylenedioxyphenylethyl)-β-phenyl-α-benzyloximinopropionamide | 53–54 | 33.7 | 6.71 | 6.67 6.52 |
| N-β-Phenethyl-α-benzyloximinopropionamide | 41–43 | [b] | 9.49 | 9.38 9.22 |

[a] *Anal.*—Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.4; H, 6.45; N, 7.53. Found: C, 77.3, 77.4; H, 6.24, 6.33; N, 7.3. Analyses done by Drs. Weiler and Strauss, Oxford, England. [b] No yield was calculated on this compound because an attempt was made to distil a portion since it showed no inclination to crystallize by the usual methods. The remaining portion, standing at room temperature for several weeks, crystallized. The portion which distilled at 184–195°/0.2 mm. did not crystallize even after standing for several months.

in toluene in the presence of phosphorus oxychloride and phosphorus pentoxide. The experiment was repeated with *p*-xylene solvent and without solvent. In another experiment, the amide was allowed to stand at room temperature for one week in phosphorus oxychloride. Another experiment at room temperature employed phosphorus pentoxide with the phosphorus oxychloride. In no case was a product isolated which had amine properties.

In light of this, an attempt was made to effect cyclization with polyphosphoric acid according to the procedure of Snyder and Werber (2). By this method the amine moiety was recovered and characterized as the picrate. From this it was assumed that the unchanged amide was hydrolyzed during decomposition of the hot reagent with ice. This was borne out by the fact that if the reaction mixture was allowed to cool before decomposition of the reagent, nothing could be isolated that had amine properties.

Experiments using polyphosphoric acid were run varying reaction time from 30 seconds to one and one-half hours at temperatures ranging from 50 to 145°, and at room temperature for one week without success.

## EXPERIMENTAL

Amides were best prepared by the procedure of Vaughan and Osato (3). The products appeared at first to be intractable oils, but a pure product was ultimately obtained by taking up the oil in methanol and adding hexane until precipitation was imminent. After 2 days to a week in the freezing compartment of the refrigerator, a solid formed which was crystallized from methanol.

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(1) Bischler, A., and Napieralski, B., *Ber.*, **26**, 1903(1893).
(2) Snyder, H. R., and Werber, F. X., *J. Am. Chem. Soc.*, **72**, 2962(1950).
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# Use of an Approximate Dielectric Constant in Solubility Studies

By WILLIS E. MOORE

THE DATA published by Autian and Udani (1) on the solubility of secobarbital have been further evaluated in terms of solubility in relation to the approximate dielectric constant (A.D.C.) of the solvent(s) by the techniques proposed by Moore (2).

This additional analysis is noted here to further illustrate the utility of using an A.D.C. in solubility studies.

The binary systems in Autian and Udani's work (their Fig. 2) were examined. Only glycerin showed a linear relationship between A.D.C. and solubility [log A.D.C. was plotted *vs.* (concentration)$^{1/2}$ of solute]. Alcohol, propylene glycol, and PEG 400 showed varying degrees of positive deviation.

The ternary systems (their Fig. 3) show linear portions in all three systems when plotted as above. The slopes differed, since solubility was different, but the intercepts were identical at a log A.D.C. value equal to an A.D.C. of 88 (see Fig. 1). This predicts a zero solubility of secobarbital in a mixed solvent with an A.D.C. of 88. This value could, of course, be meaningless. Further investigation of this relationship is required for better understanding.

Figure 1 further shows that an inconsistency appears. For example, at an A.D.C. value of 59.5 (log A.D.C. = 1.775) the solubilities of secobarbital are predicted as in Table I.

Why the solubility should vary at a constant A.D.C. but with different solvent systems cannot be explained precisely by this empirically established relationship. It is recognized that the dielectric

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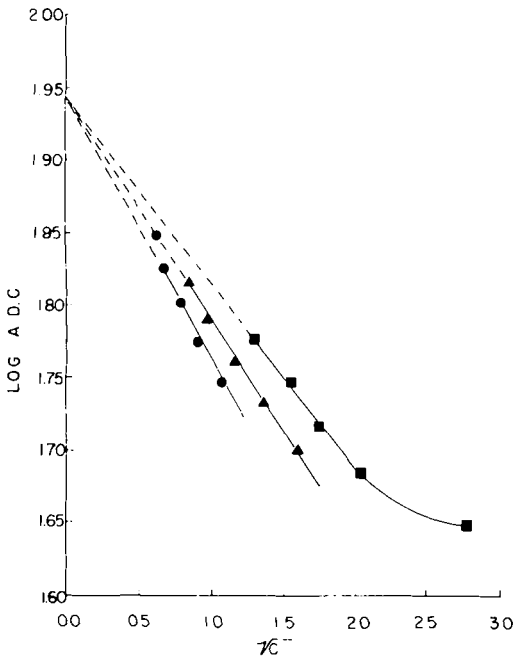



Fig. 1.—Relation of log A.D.C. to (concentration)$^{1/2}$. ●, 10% alcohol; ▲, 20% alcohol; ■, 30% alcohol.

constant of a solvent(s) system is only one factor, among many, that account for solubility.

The relationship of the apparent pKa values (their Fig. 7) for secobarbital and the A.D.C. of the solvent blend was also examined (apparent pKa was plotted *vs.* log A.D.C.). Figure 2 shows that the glycerin solvent blends were the only blends to exhibit a linear relationship. Alcohol and propylene glycol show linear portions but with positive deviations at low levels of the respective semipolar solvent. The distinctly different behavior of the PEG 400 blends is evident.

The mechanism of dissolution in aqueous blends of alcohol, propylene glycol, and glycerin may be the same (possibly solute-solvent interaction)

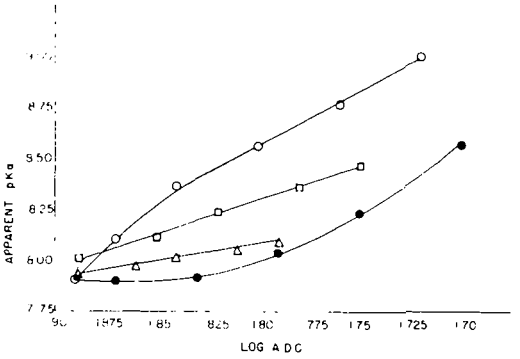



Fig. 2.—Effect of A.D.C. on pKa of secobarbital. ○, Alcohol; □, propylene glycol; △, glycerin; ●, PEG 400.

TABLE I.—PREDICTED SOLUBILITIES OF SECOBARBITAL

| % Alcohol | % Glycerin | % Water[a] | $\sqrt{C}$ | Concentration of Secobarbital, % |
|---|---|---|---|---|
| 10 | 40.0 | 50.0 | 0.94 | 0.88 |
| 20 | 25.5[a] | 54.5 | 1.10 | 1.21 |
| 30 | 10.0 | 60.0 | 1.30 | 1.70 |

[a] Estimated.

differing only in degree. The adverse effect (i.e., lowering solubility) of water on the solvent power of the "good" solvents could be due to water competing with the solute for intermolecular H-bonding with the "good" solvent rather than a polarizing (i.e., dielectric) effect.

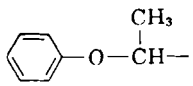
Additional experimental work such as examining the binary systems of glycerin with the other glycols and alcohol and conductance measurements of the entire series would provide further information, particularly since PEG 400 has, relatively, such a depressant effect on the ionization of secobarbital at concentrations above 40%.

REFERENCES

(1) Autian, J., and Udani, J. H., THIS JOURNAL, **49**, 376(1960).
(2) Moore, W. E., *ibid.*, **47**, 855(1958).

## ERRATUM

In the review article titled "Antibiotics. 1956–1961" (1), the structure for phenoxyethyl penicillin (phenethicillin) on page 20 should be




(1) Pratt, R., THIS JOURNAL, **51**, 1(1962).