MICROGRAM

BUREAU OF NARCOTICS AND DANGEROUS DRUGS / U.S. DEPARTMENT OF JUSTICE

Office of Science and Education
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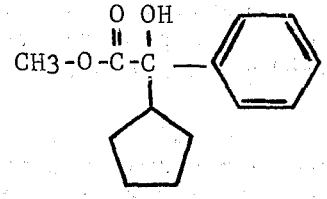
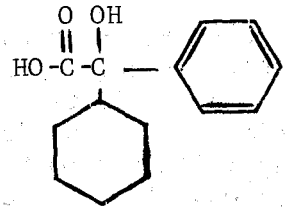
SEASON'S GREETINGS

PIPERIDYL GLYCOLATES

Recent investigations indicate that two chemicals are of interest to clandestine manufacturers. The two compounds, methylcyclopentylphenylglycolate



and cyclohexylphenylglycolic acid

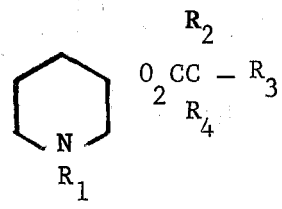


can be used to form many different piperidyl derivatives, generally referred to as the piperidyl glycolates. The piperidyl glycolates are psychotomimetic members of the piperidyl benzilate group sometimes referred to as the "JB Compounds." They are known to produce olfactory, tactile and visual hallucinations, delirium, disorientation, euphoria, and in general resemble the effects of atropine.

The piperidyl glycolates have been synthesized either by reaction of 1-alkyl-3-hydroxypiperidine with the acid chloride or the methyl ester of an appropriate acid. The reaction between 3-chloro-1-ethylpiperidine and cyclopentylphenylglycolic acid results in a mixture of the expected product (30% yield) and the ring-contracted isomer 1-ethyl-2-pyrrolidinylmethyl cyclopentylphenylglycolate (70% yield). Distillation of the

latter causes ring expansion to the former.

In a report published in Int. Rev. of Neurobiology, Vol. 4, 1962, L. G. Abood and J. H. Biel discussed at great depths the structure-activity studies they performed with the piperazine esters of glycolic acid derivatives. Using the following general structure, Abood and Biel were able to draw certain structure-activity relationships:



1. R_1 must be lower alkyl for potent CNS effects.
2. R_2 must be a hydroxyl group for maximal CNS potency.
3. R_3 should be a phenyl group. Replacement of R_3 by a propyl group greatly diminished psychotomimetic potency.
4. R_4 must be either a phenyl, thienyl, cycloalkyl, or 1-hydroxy alkyl group. In general, compounds where R_3 is phenyl and R_4 cycloalkyl possess the most potent CNS stimulating properties.
5. The position of the ester side chain or the size of the alkylene imine ring (piperidyl or pyrrolidyl) for the most part do not greatly affect CNS activity. The 3-piperidyl esters yield compounds with the most potent CNS properties, with the 2-piperidyl esters second and the 4-piperidyl derivatives last in relative effectiveness.

Abood and Biel further reported that the most potent and long-lasting psychotomimetic derivative of this class occurred where R_4 was cyclopentyl. The derivative was indicated in the New York report with cyclopentylphenylglycolate. Ditran ("JB-329") is a compound in this class, with human doses indicated to be found in the 5-10 mg. range. The synthesis of Ditran was discussed earlier in this article.

PIPERIDYL BENZILATES

Analytical information on "JB-336" (N-Methyl-3-piperidyl benzilate HCl), which appeared in Micro-Gram Vol. I, No. 9, described a screening test applicable to all esters of benzilic acid. Issue No. 10 contained additional information on the analysis and identification of JB-336. Issue No. 11 contained data on the identification of Benactyzine HCl, which is said to be "JB-313," and is known as "SAM" and "DMZ".

In a private communication, Messers Sander W. Bellman, John W. Turczan, James Heagy and Ted M. Hopes, U.S Food and Drug Administration, have furnished interesting information on elucidating the structure of JB-336, also known as "LBJ" and "TWA." See attached.

None of the piperidyl benzilate compounds are controlled under the Drug Abuse Control Amendments.

PHENCYCLIDINE HCl

This compound was the subject of a special issue of Micro-Gram, Volume I, No. 3 (January 1968), and analytical data appeared in issue No. 6 (March 1968).

At that time the capsules were being promoted on the street as the "Peace Pill" and "PCP". Later, they appeared as "Hog" and as "Cyclones."

Recently, our agents have been buying capsules promoted as tetrahydrocannabinol, and all of these on analysis have been shown to contain phencyclidine.

Now, for the first time, phencyclidine tablets have appeared on the street. These also were purported to be THC. They are mottled green (with light green, blue and brown fragments), round, biconvex, unscored, with edges slightly ridged. They are approximately 6.3 millimeters diameter, 4.37 to 4.53 millimeters thick at center and 3.2 millimeters thick at the edge. Average weight is about 137.5 milligrams. Each tablet has an irregular-shaped rough pit on one concave surface, probably due to granulation sticking to one punch face. They contained a moderate amount of phencyclidine hydrochloride with lactose monohydrate and a small amount of amorphous material.

Phencyclidine is not controlled under the Drug Abuse Control Amendments.

Mr. Paul DeZan and Mr. Robert Bianchi, U.S. Food and Drug Administration, in a private communication have furnished additional analytical data, attached.

NEW ADDRESS

The Bureau has moved from Arlington, Virginia, to 1405 Eye Street, N.W., Washington, D.C. The telephone number for the Division of Laboratory Operations is: 202 382-4692.

All mail, including material for the laboratory, should be sent to:

Division of Laboratory Operations
Bureau of Narcotics and Dangerous Drugs
1405 Eye Street N.W.
Washington, D.C. 20537

BNDD REGIONAL LABORATORY, CHICAGO

The first Bureau of Narcotics and Dangerous Drugs Laboratory is now in operation. The address is:

Chief Chemist
Regional Laboratory
Bureau of Narcotics and Dangerous Drugs
Room 725
New Post Office Building
433 West Van Buren Street
Chicago, Illinois 60607

Telephone: 312 353-3640

Mr. Jerry D. Nelson, is the Chief Chemist.

VOLUME I ENDS

This is the last issue of Volume I. Next issue, which will be Volume II, Number 1, we plan to tell you how to re-number all pages of Volume I to bring it into better conformance with the literature. We also plan to include an index to Volume I.

We wish to thank the readers who sent us information and items for Micro-Gram, and we wish to especially thank the readers from all over the World who expressed their gratitude for Micro-Gram and told us how important it is to them.

CAUTION!

Recently, a chemist commenced hallucinating after working with LSD in the laboratory. He believes that he probably inhaled the powder when he open a large container of LSD and transferred the contents while taring the net weight.

Familiarity breeds contempt, as many professionals and technicians have learned over the decades. Be aware, be cautious and use safety devices. It only takes a minute to slip on rubber gloves before handling a syringe or hypo needle, but rubber gloves will not protect you from the point of the needle if you are careless. The tools of preventive medicine, such as goggles and hoods, are always cheaper, in the long run, than are the armentarium of therapeutic medicine--doctor bills, hospital beds and medicine.

STRUCTURE ELUCIDATION OF "LBJ"

By Sander W. Bellman and John W. Turczan, New York District
and
James Heagy and Ted M. Hopes, San Francisco District

Recently, Dr. David S. Kutob, Chief of the Toxicology Section, Division of Crime Detection of the Michigan Department of Public Health, asked New York District to determine the strucuture of a hallucinogenic drug being sold in Michigan as "LBJ". The sample consisted of a hard gelatin capsule containing mostly excipients. Although there was an insufficient quantity of active ingredient for an IR or NMR spectrum, a fairly good quality mass spectrum was obtained. At the same time San Francisco District sent a drug seized by Bureau of Narcotics and Dangerous Drugs to New York District for structure determination. Its mass spectrum was the same as that for "LBJ", and there was enough sample to obtain IR and NMR spectra.

Interpretation of the combined spectra together with the chemical evidence furnished by James Heagy led to the formulation of the structure seen in Fig. 1. The chemical name of this compound is N-methyl-3-piperidylbenzilate hydrochloride; it is called JB-336 by Lakeside Laboratories, Milwaukee, Wisconsin, where it was first synthesized by Biel in 1962 (1).

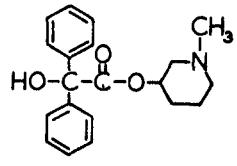


Fig. 1 - Postulated structure for "LBJ".

Experimental

Chemical Data (J. Heagy)

(a) M.p. 217.5 to 218°C dec. with evolution of gas.

(b) Positive test for chloride; when the base was extracted from ammoniacal solution with methylene chloride, a colorless, crystal-clear oil was obtained after evaporation of solvent. Adding dilute HCl and evaporating to dryness gave crystals with the same m.p. as in (a).

(c) Positive test for tertiary amines; negative test for secondary amines.

(d) Neutralization equivalent: 362.4 g/mole.

(e) Infrared spectrum similar to those of benactyzine and pipethanate.

(f) Marquis reagent gave blue color characteristic of benzilic acid and its esters.

(g) Substance was hydrolyzed with NaOH T.S. and ethanol and extracted from acid solution. Organic solvent was evaporated, yielding crystals that melted at 148-150°C and turned deep red at the higher temperature (characteristic of benzilic acid). Crystals also gave a blue color with Marquis reagent.

(h) Ultraviolet spectrum typical of non-substituted phenyl alkyls (triple peak, maximum at 257 mμ, similar to atropine).

Spectral Data

The mass spectrum was recorded on an AEI-MS-12 mass spectrometer, using a direct insertion probe. The sample was first extracted as in (b) to minimize thermal degradation in the ion source. The spectrum is shown in Fig. 2.

The infrared spectrum of the extracted material obtained on NaCl plates, using a Perkin-Elmer Model 621, is the top curve of Fig. 3, and the KBr disk spectrum of the hydrochloride salt is the bottom curve of Fig. 3.

The NMR spectra were recorded on a Varian A-60 nuclear magnetic resonance spectrometer. The free base was run in $CDCl_3$ (see Fig. 4). When trifluoroacetic acid was added to the sample in $CDCl_3$, the peak at about 5.6 ppm δ disappeared, indicating an exchangeable proton.

Discussion

From the chemical evidence, the structure shown in Fig. 5 was proposed. The molecular weight of 361.87 is in reasonably good agreement with the neutralization equivalent found, 362.4. The benzilic acid moiety is shown as unsubstituted. This might be incorrect, since the m.p. of the acid moiety found in step (g) was 148-150°C, and the literature value for benzilic acid is 180°C dec. (2). However, spectral evidence supports the proposed structure. The structure of the alcoholic portion of the ester satisfies the requirement of a tertiary amine and is suggested by the similarity of the IR spectrum with those of benactyzine and pipethanate.

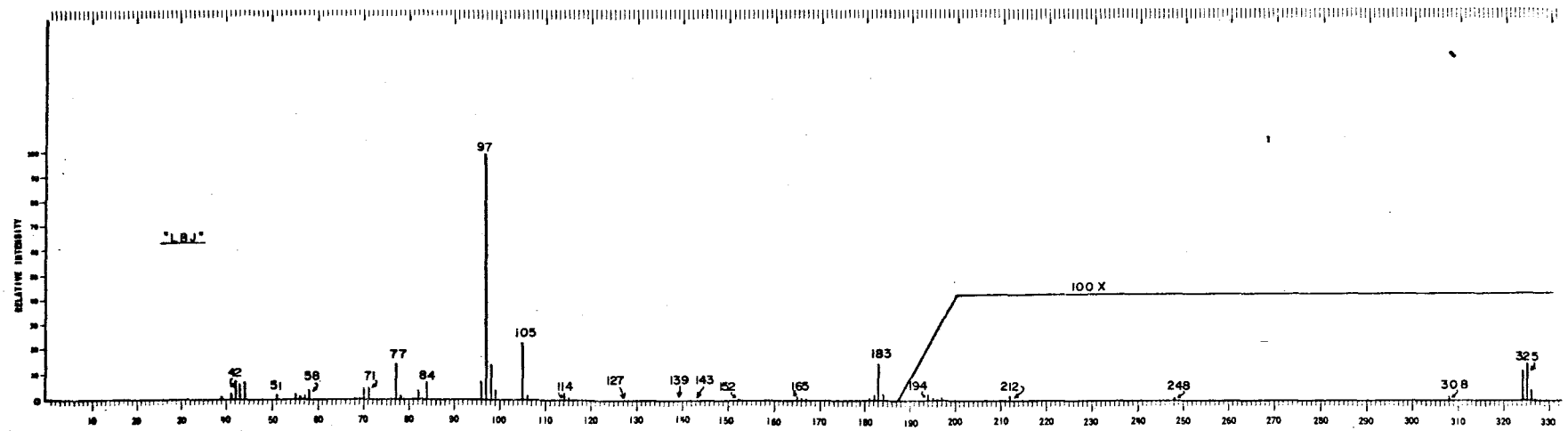


Fig. 2 - Mass spectral data for "LBJ". Note: Readings for m/e 332-400 did not show any molecular ions present and this portion of the spectrum is omitted.

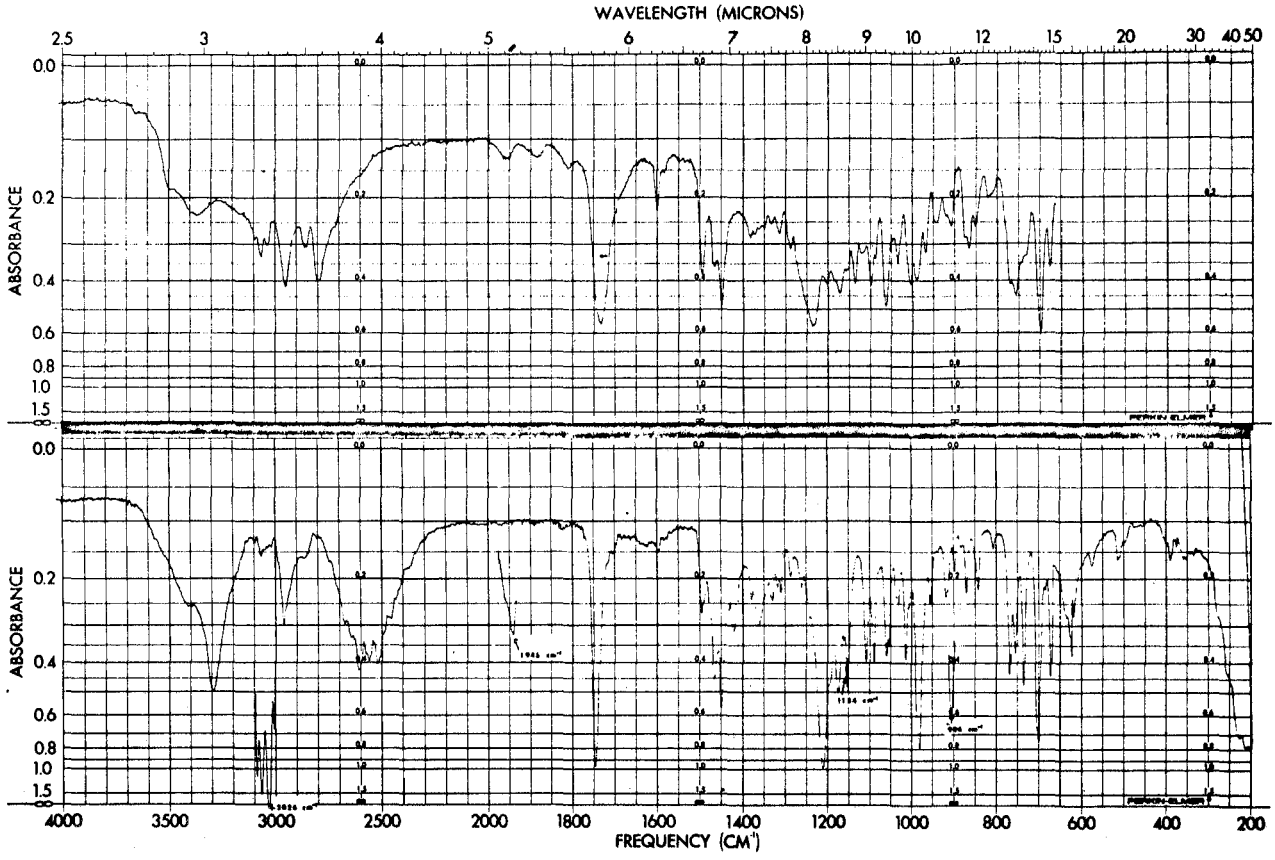


Fig. 3 - Infrared spectra of "LBJ". Top: With NaCl plates; bottom: hydrochloride salt, with KBr disk.

The IR spectrum of the free base shows a pattern in the 2000-1660 cm^{-1} range that suggests mono-aromatic substitution (3); the band at 757 cm^{-1} also confirms this hypothesis (3). The carbonyl stretching band at 1735 cm^{-1} tends to support the ester structure (4). The presence of -OH is also confirmed by the broad band at 3370 cm^{-1} (5). The spectrum of the hydrochloride salt confirms the tertiary amine hypothesis by the triplet between 2500 and 2600 cm^{-1} (6).

The mass spectrum gives a molecular ion of very low intensity at m/e 325. This would be the molecular weight of the free base of the proposed compound. The intense ion at m/e 183 is due to the $HOC(C_6H_5)_2$ ion, indicating confirmation of the unsubstituted benziloyl structure. The intense m/e 97 base peak could be $CH_2{=}CH\text{-}(NC_4H_8)$ ion. However, one should expect that some of the charge would remain on the $HOC(C_6H_5)_2COO$ ion at m/e 227. Since this is not found, it would seem, therefore, that the m/e 97 fragment is far more stable than is expected. An alternative structure that would lead to a more stable m/e 97 is contained in the six-membered methyl-piperidine ring.

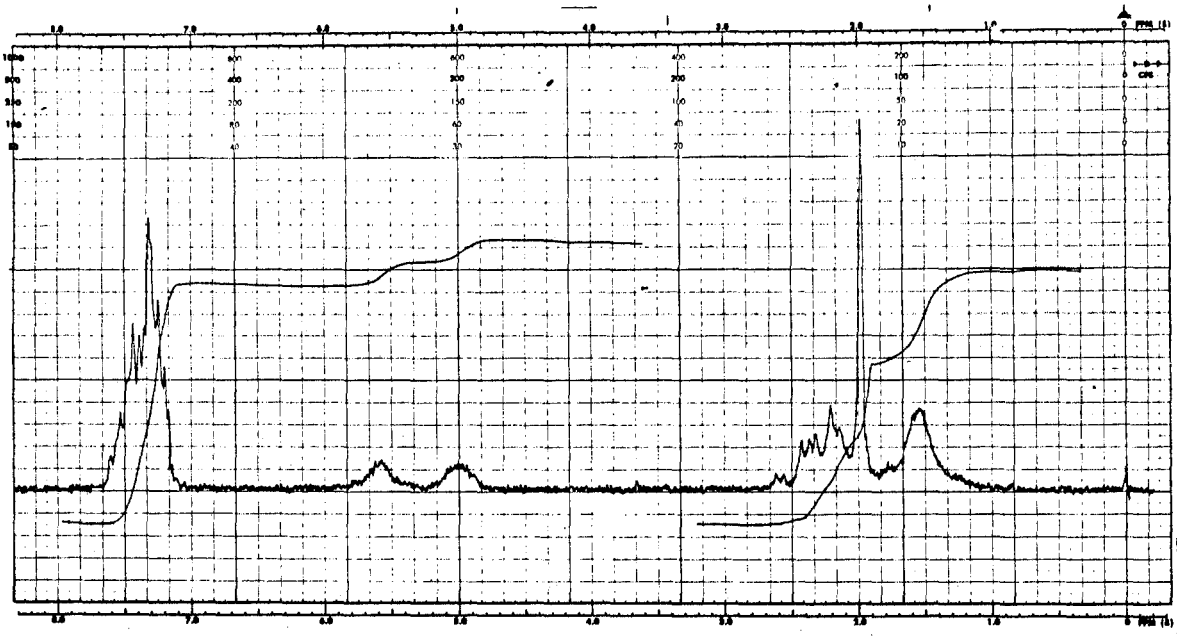


Fig. 4 - NMR spectrum of "LBJ".

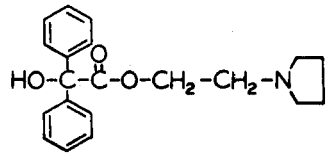


Fig. 5 - Proposed structure for "LBJ".

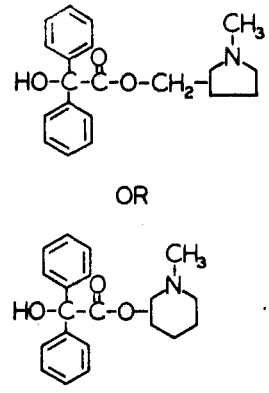


Fig. 6 - Possible structures for "LBJ", based on spectral data.

The NMR spectrum shows the presence of methyl on a ring nitrogen by the singlet at 2.2 ppm δ (7). This then alters the possible structure to those in Fig. 6. If the compound had the pyrrolidine structure, a doublet should be present at about 4.2 ppm δ. Since no doublet was observed, we considered three possible positional isomers, i.e., 2, 3, or 4-piperidylbenzilates.

N-methyl-4-piperidylbenzilate hydrochloride was purchased from Aldrich Chem. Co., Milwaukee, Wis. (No. S36379-0). Its melting point was found to be 212-213°C dec. A (1 + 1) mixture of sample and the 4-piperidyl compound had a melting point of 205°C dec. Therefore, the sample was either N-methyl-2-piperidylbenzilate or N-methyl-3-piperidylbenzilate. The NMR spectrum of the 4-isomer showed the methyne proton at 5 ppm δ (Fig. 7); the methyne proton of the sample had this same chemical shift. If the sample were the 2-isomer, this proton would be shifted further downfield. Therefore the only possibility left is N-methyl-3-piperidylbenzilate.

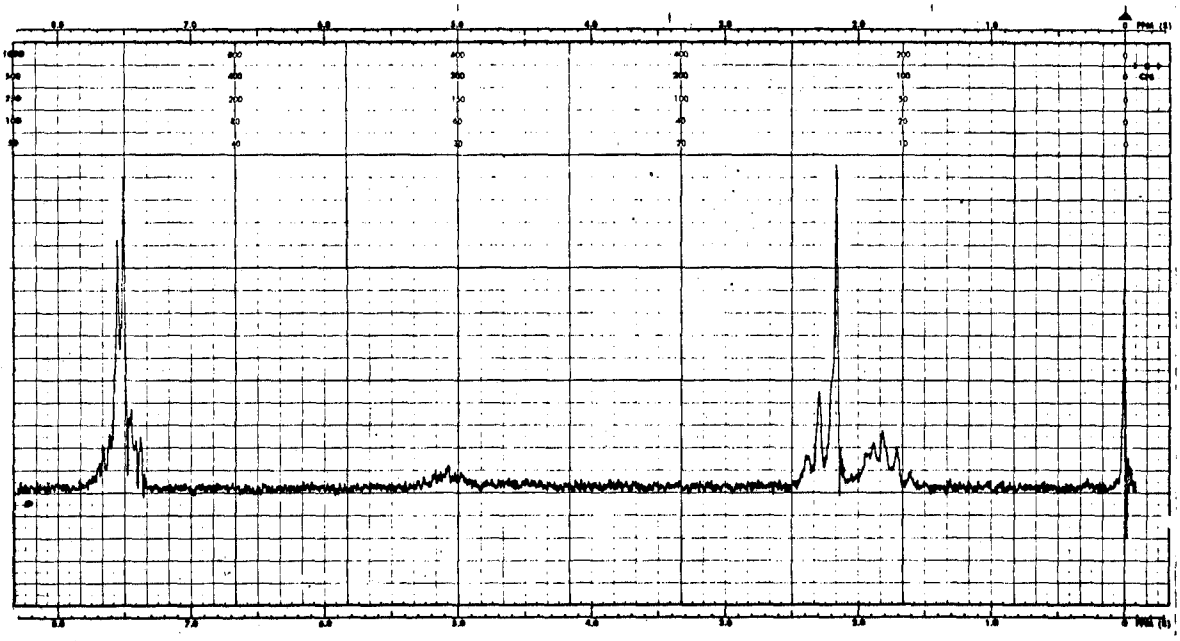


Fig. 7 - NMR spectrum of N-methyl-4-piperidylbenzilate hydrochloride.

Conclusions

By the use of conventional wet chemistry and combined spectral interpretation, "LBJ" was identified as N-methyl-3-piperidylbenzilate (JB-336). An NMR and IR spectrum of JB-336 run by S. Koch, DPS, finally confirmed the identification.

General Discussion of the Use of Combined Spectral Analysis for Identification of Unknown Substances (S.W. Bellman and J.W. Turczan)

In the past year New York District has received over 25 requests for the identification of unknown substances by mass spectrometry and nuclear magnetic resonance. When the submitted material had not been

previously analyzed, a tentative assignment of structure was made without the use of a reference standard material. These structures were subsequently verified by comparison with available authentic compounds.

These requests were in four general categories: identification of contaminants in drugs; identification of incorrectly labeled drugs; confirmation of the identity of pesticide residues found by GLC; and identification of hallucinogenic drugs seized under provisions of the Drug Abuse Control Amendment.

Examples of the first three categories are cited below:

(1) 2,2'-Dithiobisbenzothiazole, a compound used in the vulcanization of rubber, was found in a vitamin B_{12} injection. Mass spectrometry and reference to the Sadtler Infrared Index were used for its identification.

(2) A sample of imported medicated feed was collected on suspicion of its being a smuggled hallucinogenic drug. Mass spectrometry, NMR, IR, and optical crystallography, however, identified the substance as pure chloramphenicol.

(3) Hexachlorobenzene was tentatively identified in eggs by GLC. Since this pesticide is not usually found in eggs a more specific identification was needed. The Florisil column eluate was concentrated and submitted to mass spectral analysis. Mass spectrometry did confirm the identity of hexachlorobenzene. Although the Florisil column extract was clean enough in this case, direct GLC trapping techniques would insure sample cleanliness in more general cases.

These are just a few of the many examples of these first three categories, but most of the identification work we have done has been on hallucinogenic drugs. In June 1967, Division of Pharmaceutical Sciences asked our help in the identification of the then unknown compound, STP. The combined use of IR, NMR, and mass spectrometry, as well as previous work by Thomas Alexander and his group, showed that the compound was methyldimethoxyphenylisopropylamine. The only item undetermined was the relative positions of the substitutents around the phenyl nucleus. Later the compound was found to be 4-methyl-2,5-dimethoxyphenylisopropylamine. Since that time, combined spectral analysis has been used to identify several other hallucinogenic drugs and reaction intermediates seized during raids, in addition to the identification of LBJ and STP, mentioned previously. The compounds are monoethyltryptamine; X-methyldiethyltryptamine (X is probably 2); 2-(3,4,5-trimethoxyphenyl)-2-hydroxyethylamine; 3,4-methylenedioxyamphetamine (MDA); 1,2-methylenedioxy-4-(2-nitropropenyl) benzene; 3,4-methylenedioxybenzaldehyde (piperonal); 3-indolylglyoxyldimethylamide; 3-indolylglyoxyldiethylamide; methyl-3,4,5 trimethoxybenzoate; N-methyl-4-piperidylbenzilate; 3,4,5-trimethoxybenzaldehyde; and 3-indolylglyoxyldibenzylamide.

The above results show that a combined spectral interpretation technique, utilizing IR, UV, NMR, and mass spectrometry, can be a valuable tool in the structure elucidation of unknown compounds encountered in food and drug activities. It is our belief that a mass spectrometer and NMR spectrometer would be a valuable addition to any District laboratory, especially one engaged in the identification of unknown drugs. A compilation of UV, IR, NMR, and mass spectra and applicable optical rotary dispersion curves, cross indexed, of hallucinogenic drugs, isolable reaction intermediates, and starting materials used in their synthesis is being prepared. This forthcoming compilation of spectra should reduce the time needed for spectral interpretation, even for those laboratories that do not have NMR and mass spectrometers.

Acknowledgments

The authors wish to acknowledge the contributions of Theodore Kram, Paul DeZan, and Richard Fox, New York District Laboratory, who have assisted in the interpretation of the combined spectra. Leonora Auerbach performed the optical crystallography tests.

References

(1) Biel, J.H., U.S. Patent 2,995,492; thru Chem. Abstr. 56, 4736f (1962).

(2) Handbook of Chemistry and Physics, 46th Ed., Chemical Rubber Co., Cleveland, Ohio, 1965-1966, p. C-93.

(3) Nakanishi, K., Infrared Absorption Spectroscopy-Practical, Holden-Day, Inc., San Francisco, 1962, p. 27.

(4) Ibid., p. 44.

(5) Ibid., p. 30.

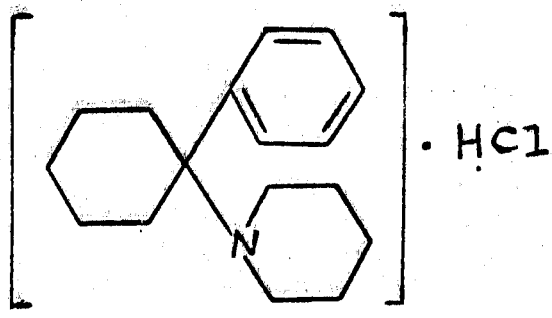
(6) Ibid., p. 39.

(7) Hammer, C.F., "NMR Chemical Shifts", Georgetown University, Washington, D.C., 1966.

ANALYSIS AND IDENTIFICATION OF PHENCYCLIDINE HYDROCHLORIDE (PCP,SERNYL)

Paul De Zan and Robert Bianchi
New York District
U.S. Food and Drug Administration

A number of BNDD samples suspected of being THC have been received at the New York District laboratory. However, THC (tetrahydrocannabinol) was not detected in any of the samples. Instead, Phencyclidine Hydrochloride [1-(1-phenylcyclohexyl) - piperidine hydrochloride] was found to be the active ingredient.



$C_{17}H_{25}N.HCl$ Mol. Wt.=279.86

PHENCYCLIDINE HYDROCHLORIDE

Physical Properties

(a) Hydrochloride:

Description - white, crystalline powder

Solubility - soluble in chloroform, methylene chloride, water insoluble in ether.

Melting Point - 230 - 231°C

(b) Free Base:

Description - white crystalline powder

Melting Point - 46 - 46.5°C (Merck Index)

Qualitative Test (Modified Feigl test for tertiary amines):

Reagent: 5 mls of Acetic Anhydride to which is added about 200 mgs citric acid (Not all the acid may dissolve since solution will become saturated)

Since carbonates interfere, a portion of the capsule powder must be dry extracted with chloroform and evaporate to dryness in a small porcelain crucible. Add 0.5- 1 ml of the prepared reagent, cover with a watch glass and heat on a steam bath for about 3 minutes. A red - violet color indicates the presence of PCP.

Method of Analysis

Column Preparation: Mix unformly about 2 gms of acid washed celite with 1 ml 0.1N HCl and transfer to a chromatographic column containing a glass wool plug.

Procedure: Accurately weigh about one-third of a dosage unit (average dosage unit appears to be 4-5 mgs PCP) into a 50 ml beaker. Add 2 mls of 0.1N HCl and 3 gms of celite and stir thoroughly until the mass appears uniform. Quantitatively transfer the material to the chromatographic column through a powder funnel. Scrub the beaker with a piece of glass wool, transferring all particles and the glass wool into the column.

Elute the column with 50 mls of ether and discard the eluant. Just prior to the ether solvent level passing into the column, add 60 mls of chloroform and begin collecting the eluate. Rinse the stem of the tube with a small amount of chloroform.

Evaporate the chloroform to dryness on a steam bath. Add 3.0 mls 0.1N HCl to the residue and scan the solution on a suitable spectrophotomer. Compare against a standard solution containing 1 mg PCP per 3 mls 0.1N HCl. Use the 262 mu peak for quantitation.

Identification by IR Spectrophotometry:

Transfer the solution (used for quantitation) into a 30 ml separatory funnel and extract with 3 x 10 ml portions of chloroform. Evaporate the chloroform to dryness. Add 2 ml of anhydrous ether to the residue and re-evaporate to dryness. Prepare a KBr disc of the dry residue. Obtain the infrared absorption curve and compare to that of a standard curve for Phencyclidine Hydrochloride.

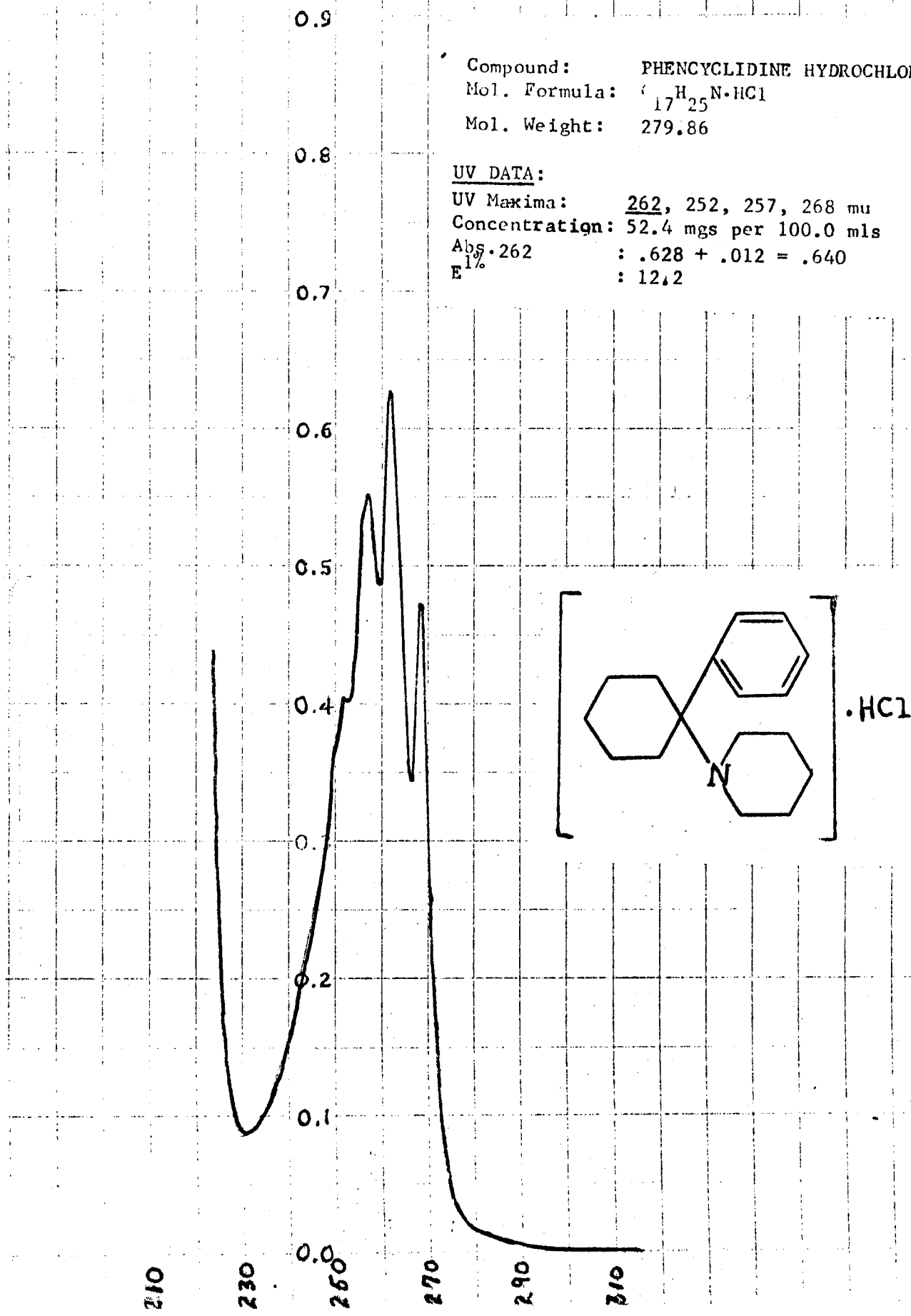
A potassium bromide pellet was prepared and an IR spectrum run. The spectrum resembled that of carbowax 6000, a polyethylene oxide polymer, as verified by comparison with a spectrum ofthe standard material.

Methyphenidate: The acid layer was made distinctly alkaline with 50% sodium hydroxide and extracted with 20 ml ethyl ether. The ethereal extract was washed three thimes with 20 ml water, then filtered through cotton into small beaker. Added 2 - 3 drops acetone saturated with oxalic acid and stirred vigorously, scratching beaker walls to effect precipitation; filtered and dried same way as other precipitate, but using ethyl ether as wash solvent.

Methylphenidate hydrochloride standard was treated similary; nujol mulls of sample and standard derivatives produced identical IR spectra.

Compound: PHENCYCLIDINE HYDROCHLORIDE
Mol. Formula: $C_{17}H_{25}N \cdot HCl$
Mol. Weight: 279.86

UV DATA:
UV Maxima: 262, 252, 257, 268 mu
Concentration: 52.4 mgs per 100.0 mls
Abs.262 : .628 + .012 = .640
$E^{1\%}$: 12.2



10-18-68
(KBr)
PHENCYCLIDINE
HYDROCHLORIDE
KBr
50%
HCl

SPOT TEST FOR AMPHETAMINE

Donald L. Frasch
State Chemical Laboratories
Vermillion, South Dakota

Reagent : 1 ml formaldhyde in 20 cc sulfuric acid

Procedure: Place a small amount of powdered material in a spot plate and add one to two drops of the above reagent. After the orange color characteristic of amphetamine has appeared, place spot plate under a uv light. The addition of a few drops of water will produce a blue-green fluoresce.

Any interference from "Placidyl" fluorescence is present before addition of the water.

Salicylic acid also gives a positive test, but with a slightly different shade in color and with some precipitation in the solution.